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TRANSACTIONS OF THE

SECTION ON

Dermatology and Syphilology

of the
American Medical Association
at the Seventy-Third Annual
Session, held at St. Louis, Mo.,
May 22 to 26, 1922

AMERICAN MEDICAL ASSOCIATION PRESS
CHICAGO: NINETEEN HUNDRED AND TWENTY-TWO

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LIST OF OFFICERS

This section was organized in 1887 and has been served by the following officers, the year being the date of election. The list is compiled from the published records, which are incomplete in some cases. It will be appreciated if any errors are brought to the attention of the Secretary of the American Medical Association.

SECTION ON DERMATOLOGY AND SYPHILOLOGY

1887 Chairman, L. D. Bulkley, New York.
Secretary, F. F. Dunlop, Kentucky.

1888 Chairman, L. D. Bulkley, New York.
Secretary, W. T. Corlett, Cleveland.

1889 Chairman, J. E. Atkinson, Baltimore.
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1892 Chairman, L. A. Duhring, Philadelphia.
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1894 Chairman, A. E. Regensburger, San Francisco.
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SECTION ON CUTANEOUS MEDICINE AND SURGERY

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Sceretary, J. M. Blaine, Denver.

1899 Chairman, L. D. Bulkley, New York.
Secretary, R. R. Campbell Chicago.

1900 Chairman, W. L. Baum, Chicago.
Secretary, R. R. Campbell Chicago.

1901 Chairman, H. W. Stelwagon, Philadelphia.
Secretary, R. R. Campbell Chicago.

1902 Chairman, John A. Fordyce, New York.
Secretary, R. R. Campbell Chicago.
Delegates, M. B. Hartzell, Philadelphia, and William L. Baum, Chicago.

1903 Chairman, Henry G. Anthony, Chicago.
Secretary, R. R. Campbell Chicago.
Delegates, Jay F. Schamberg, Philadelphia.

1904 *Chairman, Douglas W. Montgomery, San Francisco.
Secretary, R. R. Campbell Chicago.
Delegate, A. W. Brayton, Indianapolis.

1905 (The Section did not meet and the old officers acted two years.)

1906 Chairman, R. R. Campbell, Chicago.
Secretary, M. L. Heidingsfeld, Cincinnati.
Delegate, Henry R. Varney, Detroit.

* Owing to the absence of the chairman and the secretary, Dr. Ludwig Weiss of New York and Dr. M. L. Heidingsfeld of Cincinnati were appointed temporary chairman and temporary secretary, respectively.

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LIST OF OFFICERS—Continued

1907 Chairman, M. B. Hartzell, Philadelphia.
Secretary, M. L. Heidingsfeld, Cincinnati.
Delegate, R. R. Campbell, Chicago.

1908 Chairman, William Allen Pusey, Chicago.
Secretary, M. L. Heidingsfeld, Cincinnati.
Delegate, R. R. Campbell, Chicago.

SECTION ON DERMATOLOGY

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1910 Chairman, Charles J. White, Boston.
Vice Chairman, Martin F. Engman, St. Louis.
Secretary, H. R. Varney, Detroit.

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1917 Chairman, Henry H. Hazen, Washington, D. C.
Vice Chairman, Ernest Dwight Chipman, San Francisco.
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Delegate, Sigmund Pollitzer, New York.

1918 Chairman, Otto H. Foerster, Milwaukee.
Vice Chairman, David Lieberthal, Chicago.
Secretary, Walter J. Highman, New York.
Delegate, George M. MacKee, New York.

1919 Chairman, Oliver S. Ormsby, Chicago.
Vice Chairman, John E. Lane, New Haven, Conn.
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Delegate, George M. MacKee, New York.

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1921 Chairman, Ernest D. Chipman, San Francisco.
Vice Chairman, Harry D. Irvine, Minneapolis.
Secretary, Harold N. Cole, Cleveland.
Delegate, Howard Fox, New York.

1922 Chairman, Marcus Haase, Memphis, Tenn.
Vice Chairman, Frank W. Cregor, Indianapolis.
Secretary, Harold N. Cole, Cleveland.
Delegate, Walter J. Highman, New York.

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PROCEEDINGS OF THE SECTION

WEDNESDAY, MAY 24—MORNING

The meeting was called to order at 9:15 by the chairman, Dr. Ernest Dwight Chipman, San Francisco.

Dr. Ernest Dwight Chipman, San Francisco, read the chairman's address.

The following papers were read as a symposium on "Syphilis":

Dr. James R. Driver, Cleveland: "A Study of Four Hundred and Eighty-Five Cases with Genital Lesions."

Drs. H. L. Keim and Udo J. Wile, Ann Arbor, Mich.: "The Kahn Precipitin Test in the Diagnosis of Syphilis."

Dr. Albert Keidel, Baltimore: "Studies in Asymptomatic Neurosyphilis, IV, The Apparent Rôle of Immunity in the Genesis of Neurosyphilis."

Drs. E. C. White, J. H. Hill, J. E. Moore and H. H. Young, Baltimore: "A New Mercurial for the Intravenous Treatment of Syphilis: First report of Chemical, Animal and Clinical Experiments and Results."

These four papers were discussed by Drs. Udo J. Wile, Ann Arbor, Mich.; James Herbert Mitchell, Chicago; Richard L. Sutton, Kansas City, Mo.; John E. Lane, New Haven, Conn.; Harry G. Irvine, Minneapolis; William Allen Pusey, Chicago; Joseph Grindon, St. Louis; Victor G. Vecki, San Francisco; F. W. Cregor, Indianapolis; James R. Driver, Cleveland; H. L. Keim, Ann Arbor, Mich.; Albert Keidel, Baltimore, and J. E. Moore, Baltimore.

The chairman appointed Dr. H. G. Irvine, Minneapolis, and Dr. William T. Corlett, Cleveland, to serve on the Executive Committee in the places of Dr. Walter J. Highman, New York, and Dr. Oliver S. Ormsby, Chicago, who were absent.

The resolution referred to in the minutes of the Section on Practice of Medicine was offered, and, after discussion, was adopted.

WHEREAS, It has always been the right of the Scientific Sections to have representation through a properly constituted delegate for the purpose of correlating with the aims and purposes of the Association, the special interests of each individual section, and

WHEREAS, The section delegates contribute to the deliberations of the House of Delegates, the crystallized opinions which have evolved from the scientific proceedings of each particular section, and

WHEREAS, This is the only point of immediate contact of the great mass of the Fellows of the American Medical Association who assemble at our annual session, with the legislative body—the House of Delegates; therefore, be it

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Resolved, That we, members and Fellows of the Association, assembled in a meeting of the Section on Practice of Medicine, do hereby protest against this attempt to completely separate the scientific from the legislative branch of the Association.

Dr. Herman Goodman, New York, read a paper on "Ulcerating Granuloma (Granuloma Inguinale). Discussed by Drs. Joseph Grindon, St. Louis; A. J. Markley, Denver; Jeffrey C. Michael, Houston, Texas; William Litterer, Nashville, Tenn.; Jesse B. Shelmire, Dallas, Texas; Harold N. Cole, Cleveland; Earl D. Crutchfield, Galveston, Texas, and Herman Goodman, New York.

The President, Dr. George E. de Schweinitz, and the retiring President, Dr. Hubert Work, addressed the section.

Dr. Frank W. Cregor, Indianapolis, read a paper on "Sporotrichosis." Discussed by Drs. Richard L. Sutton, Kansas City, Mo.; J. M. King, Nashville, Tenn.; Everett S. Lain, Oklahoma City; John H. King, Nashville, Tenn., and Frank W. Cregor, Indianapolis.

Dr. Erwin P. Zeisler, Chicago, read a paper on "Pityriasis Rubra Pilaris—Familial Type." Discussed by Drs. Richard L. Sutton, Kansas City, Mo.; Harold N. Cole, Cleveland; David Lieberthal, Chicago; William Allen Pusey, Chicago, and Erwin P. Zeisler, Chicago.

Thursday, May 25—Morning

The meeting was called to order at 9:10 by the chairman, Dr. Ernest Dwight Chipman, San Francisco.

Dr. Moses Scholtz, Los Angeles, read a paper on "Lupus Erythematosus Acutus Disseminatus Hemorrhagicus." Discussed by Drs. W. H. Goeckerman, Rochester, Minn.; Everett S. Lain, Oklahoma City; William T. Corlett, Cleveland; Marcus Haase, Memphis, Tenn.; William Frick, Kansas City, Mo.; Richard L. Sutton, Kansas City, Mo., and Moses Scholtz, Los Angeles.

Drs. H. H. Hazen and F. J. Eichenlaub, Washington, D. C., presented a paper on "Leukoplakia." Discussed by Drs. F. E. Senear, Chicago, William H. Guy, Pittsburgh; J. M. King, Nashville, Tenn.; William T. Corlett, Cleveland; I. L. McGlasson, San Antonio, Texas; Erwin P. Zeisler, Chicago; W. H. Goeckerman, Rochester, Minn., and F. J. Eichenlaub, Washington, D. C.

Drs. Marcus Haase, Clement H. Marshall and E. R. Hall, Memphis, Tenn., presented a paper on "Local Blastomycosis." Discussed by Drs. F. E. Senear, Chicago; Louis E. Schmidt, Chicago; Ernest D. Chipman, San Francisco; J. M. King, Nashville, Tenn.; Earl D. Crutchfield, Galveston, Texas; Harold N. Cole, Cleveland, and Clement R. Marshall, Memphis, Tenn.

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Drs. Howard I. Morrow, Ernest L. Walker and Hiram E. Miller, San Francisco, presented a paper on "Experience with Chaulmoogra Oil Derivatives in the Treatment of Leprosy at San Francisco." Discussed by Drs. William T. Corlett, Cleveland; R. M. Wilson, Kwangju, Korea; I. L. McGlasson, San Antonio, Texas; Ernest D. Chipman San Francisco; Floyd Stewart, St. Louis; Edward A. Oliver, Chicago, and Hiram E. Miller, San Francisco.

Mr. C. N. Moore, Schenectady, N. Y., read a paper on "The Physical Principles Underlying the Development of High Voltage Roentgen-Ray Apparatus." Discussed by Drs. William Allen Pusey, Chicago; Harold N. Cole, Cleveland; F. J. Eichenlaub, Washington, D. C., and William H. Guy, Pittsburgh, and Mr. C. N. Moore, Schenectady, N. Y.

Dr. C. Guy Lane, Boston, read a paper on "Industrial Dermatoses at the Massachusetts General Hospital." Discussed by Drs. Richard L. Sutton, Kansas City, Mo.; Joseph Grindon, St. Louis; Jeffrey Michael, Houston, Texas; Moses Scholtz, Los Angeles; T. J. Burke, Pittsburgh; William Allen Pusey, Chicago; C. H. Ball, Tulsa, Okla.; L. S. Ayres, Los Angeles; Lester Hollander, Pittsburgh; A. J. Markley, Denver; David Lieberthal, Chicago, and C. Guy Lane, Boston.

Dr. W. H. Goeckerman, Rochester, Minn., read a paper on "A Peculiar Discoloration of the Skin Probably Resulting from Mercurial Compounds (Calomel) in Proprietary Face Creams." Discussed by Drs. F. J. Eichenlaub, Washington, D. C.; Richard L. Sutton Kansas City, Mo.; J. M. King, Nashville, Tenn.; Ernest D. Chipman, San Francisco; Edwin P. Zeisler, Chicago, and W. H. Goeckerman, Rochester, Minn.

Friday, May 26—Morning

The meeting was called to order at 9:10 by the chairman, Dr. Ernest Dwight Chipman, San Francisco.

The following officers were elected: chairman, Dr. Marcus Haase, Memphis, Tenn.; vice chairman, Dr. Frank W. Cregor, Indianapolis; secretary, Dr. Harold N. Cole, Cleveland; delegate, Dr. Walter J. Highman, New York; alternate, Dr. Everett S. Lain, Oklahoma City.

Dr. William Allen Pusey moved that the chairman appoint a committee of one to work in conjunction with a committee from the Sections on the Practice of Medicine, Urology, Nervous and Mental Diseases, Pathology and Physiology and Pediatrics on a standardization of the Wassermann test.

This motion was seconded by several members and unanimously carried.

The chairman appointed Dr. Martin F. Engman, St. Louis, to represent the Section on Dermatology and Syphilology on this committee.

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The following papers were read as a symposium on "Malignancy":

Dr. Howard James Parkhurst, Toledo, Ohio: "The Tissue Reaction in Malignant Epitheliomas of the Skin: Its Value in Diagnosis and in Prognosis."

Drs. Walter J. Highman and Ray H. Rulison, New York: "Expectancy in Roentgen Treatment of Skin Lesions from the Pathologic Standpoint."

Dr. Laurence Taussig, San Francisco: "Carcinoma of the Tongue and Its Treatment with Radium."

Dr. Joseph C. Bloodgood, Baltimore: "Surgical Treatment of Cancer of the Lip."

Dr. G. E. Pfahler, Philadelphia: "Treatment of Cancer of the Lip by Electrocoagulation."

Dr. Everett S. Lain, Oklahoma City: "The Treatment of Cancer of the Lip by Radiotherapy."

These six papers were discussed by Drs. Gordon B. New, Rochester, Minn.; Joseph C. Bloodgood, Baltimore; F. J. Eichenlaub, Washington, D. C.; William H. Guy, Pittsburgh; Richard L. Sutton, Kansas City, Mo.; G. A. Wyeth, New York; C. H. Ball, Tulsa, Okla.; T. C. Kennedy, Indianapolis; Frank W. Cregor, Indianapolis; John Howard King, Nashville, Tenn.; Moses Scholtz, Los Angeles; I. L. McGlasson, San Antonio, Texas; Davis W. Goldstein, Fort Smith, Ark; Earl D. Crutchfield, Galveston, Texas; Ben R. Kirkendall, Columbus, Ohio; H. J. Parkhurst, Toledo, Ohio; R. H. Rulison, New York; Laurence Taussig, San Francisco; George E. Pfahler, Philadelphia, and Everett S. Lain, Oklahoma City.

Dr. Marcus Haase, Memphis, moved a rising vote of thanks to the officers of the section for the considerate and courteous treatment accorded the members, and to the St. Louis profession for their excellent clinic and generous hospitality. This motion was seconded and unanimously carried.

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THE NEEDS AND DUTIES OF DERMATOLOGY *

ERNEST DWIGHT CHIPMAN, M.D.
SAN FRANCISCO

As prelude to a strictly scientific program, it seems fitting that the chairman's address should deal with some of the more general considerations which concern dermatology as a specialty. There are many topics deserving of careful thought, but nothing is more timely, perhaps, than a résumé of our needs and duties.

In a general sense, our greatest need is efficiency, and our paramount duty is service. Efficiency and service are closely related, because the greater our efficiency, the greater our capacity for service.

The question of efficiency should interest us with respect to both immediate and future requirements. It were well that we plan somewhat for the dermatology of tomorrow, even while seeking to better that of today.

We must all be aware of the growing sentiment toward standardization in the specialties. We have been, and we are now, living in an age of self-styled specialists. The specialist is as easily made as home-brew and is of equally harmful potential. The only criterion of proficiency is recognition by fellow practitioners of one's own branch. Such recognition may take the form of election to a national society. This is not necessarily conclusive, for good men are sometimes passed by and indifferent ones chosen. Under present conditions, the national societies have an opportunity of rendering infinitely useful service. This, I believe, they are for the most part doing; but it is self-evident that, properly to function in this respect, they must

* Chairman's Address.

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resolutely avoid anything which savors of personal animosity, racial antipathy, nepotism or friendly predilection.

The fact that specialism is entered so easily and through so many channels does not make for uniformity of standards. Whatever may be said against a wider application of the elective system for the undergraduate medical students, it seems obvious that those who intend to specialize should be given the greatest latitude in their intern year.

If the well-educated man is one who knows everything about something and something about everything, the well-trained specialist is one who knows everything about his own department and something about all the others. So that, however zealously we may strive for perfection in one line, it must not be at the expense of broad general training. Specialism of today is justly criticized on the ground of a tendency toward narrowness. The reason for this criticism should be absolutely removed.

Postgraduate colleges as conducted today undoubtedly perform valuable service. The casual course of six weeks does not, however, equip one for a specialty. What seems an urgent need is the designation by unquestioned institutions which will give the same standing to the specialist that the M.D. degree gives the general practitioner.

What about our own case? Of course we need more efficiency. We are quite conscious of our shortcomings. And obviously, by the development of personal attributes, we may work to a higher plane of excellence. But if dermatology as a specialty needs more efficiency, it needs also the means whereby it is to be attained. We shall find those means when we find truth. If we would be really effective, we must find the truth that so often is hidden from us.

What is the truth about dermatitis herpetiformis, or psoriasis, or lupus erythematosus or vitiligo? What is

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the truth about many of the dermatoses which we bedeck with names that suggest so much wisdom and conceal such appalling ignorance? Our real, our urgent, our vital need is truth; to know what causes all these diseases with the long names.

Our duty in the premises is apparent enough. Both as individuals and as a section, we should do our utmost toward the solution of the problems of etiology, which constitute, today, our most serious handicap.

There are many promising fields for research. Among the external agencies, the part played by fungi has probably by no means been realized. Concerning possible internal causes, we have gone through so many disappointing experiences with various hypotheses that the mildest suggestion of novelty in etiology at once provokes violent reaction.

However much may be said in favor of a certain degree of enlightened skepticism, we must not, through fear of an overswung pendulum, allow the clock to run down. We have need of open minds. The truth that we are seeking will not be found in the reactionary spirit which mistakes enthusiasm for fanaticism, nor will it be found in the exuberant spirit of faddism. Probably it will be found somewhere between the two.

In our search for etiologic factors, we now have a list of possibilities, most of which belong exclusively to the present generation. It is our duty to exploit them without preconceptions as to their validity. I believe that it is fair to propound the following as worthy of complete investigation in every dermatosis of unknown origin: focal infection, the sympathetic nervous system, the endocrine glands, protein sensitization and disturbed metabolism. It seems not unreasonable to suppose that such investigation will add materially to our store of etiologic knowledge.

Now, as to our duties. Granting that our chief duty is service, we may consider it under three heads: (1) service to individual patients; (2) service to society in general, and (3) service to the medical profession.

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The most valuable service which the dermatologist can perform for the individual is the interpretation of the cutaneous lesion. Too often the careless view is held that the skin specialist is solely concerned with superficial lesions of cosmetic importance only. It is true of course that many consultations are for the relief of relatively innocuous disorders; but it is equally true that many of the lesions for which relief is sought, in the belief that they are trivial, represent boundary posts on the frontier of serious disease.

The interpretation of a given lesion may mean the simple diagnosis of some definite disease, or the recognition of some constitutional condition which, for the moment, is giving rise to no signs or symptoms elsewhere.

In such serious conditions as the acute exanthems, precancerous or frankly malignant lesions, and the various forms of tuberculosis, leprosy or syphilis, the diagnosis practically carries its own interpretation. There is a large group, however, in which slight cutaneous lesions may signify some grave constitutional condition. It is here that we may perform service of utmost value to the individual, if we are complete and accurate in our interpretations.

Some lesions point to diabetes, some to cardiac disturbances, some to pelvic disorder, some to the endocrines, and some suggest toxemia, the search for which leads to focal infection.

The point cannot be made clearer, perhaps, than by taking, as an example, a case of lupus erythematosus. I do not believe that we are doing our full duty in any case of lupus erythematosus in which we are content with a diagnosis plus even successful local treatment. Lupus erythematosus is so definitely suggestive of toxemia that, whether it be from a tuberculous lesion or an infection in the antrum, we have not satisfied the moral obligation which we assume in taking the case, unless, in addition to the treatment, we

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take on the burden of interpreting the lesions in the most complete sense that available evidence allows. If we find, for example, an infection of the antrum, we must assume that, whether or not it be in etiologic relation with the cutaneous lesions, it is a potential source of danger, about which it is our duty to advise. It is only through the adoption of such an attitude that we can hope to give the same service that we would wish to receive were we in the place of the patient. This, after all, would seem to be a fair criterion of service.

The medical profession has definite duties to society, in which all the specialties must participate according to their respective abilities. No obligation is more important than the conservation of public health. Aside from work along broad lines of general preventive medicine, in various aspects of which dermatology is vitally interested, we can serve humanity to no better purpose than in the exposure of quackery.

Quackery flourishes on nothing so much as on ignorance. The fallacies of former generations concerning the nature of skin diseases still linger in the popular mind, which even today is prone to regard any eruption as evidence of impurity of blood or the stigma of personal or ancestral vice.

These misconceptions make a particularly favorable soil for the development of quackery. The desire for beauty is also a human weakness which is bounteously catered to in the exploitation of innumerable alleged aids to cosmetic perfection. No one knows better than the dermatologist the heavy toll paid by the sufferers from paraffin oil injections; no one knows better the needless unhappiness from experiences with noxious hair dyes, hair removers and even hair growers.

To us, the duty is clear. It is simply the diffusion of truth. In California, a good start has been made by a medical organization which is called the League for the Conservation of Public Health.

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One of its activities along educational lines is in cooperation with two daily newspapers which devote certain space to medical information. Questions are referred through the league to the medical man who is deemed an authority in the subject involved. These newspapers are also furnished with various medical articles written by specialists. Both in Los Angeles and in San Francisco, it is now possible for the layman to obtain authoritative opinion or guidance concerning any medical problem. Thus, our profession is attempting, in some measure, to fulfil its obligation to the community, with respect both to preventive medicine and to quackery.

The duty of dermatology to the profession is cooperation. While this is necessarily a reciprocal relation, we shall do our part by attempting to keep in closer touch with medicine in general, as well as by correlating our findings with those of internists and of specialists in other lines. We owe it to the profession to make known in plain terms the significance of dermatologic lesions as we interpret them. We need to write for the man in general practice as well as for our confrères in dermatology.

We need to make of dermatology a clearing house for the subject of syphilis. While we recognize the interest of the internist and the specialist in other branches, we must insist that the teaching and treatment of this disease is today, as in former times, an integral part of dermatology. Before the development of the Wassermann test, there was never doubt as to the destination of a syphilitic patient. Because of the training of dermatologists in the recognition of the objective signs of the disease, the matter was by common consent left in their hands. Today, syphilis is diagnosed in the laboratory and is treated by any or by all. It is our duty to demonstrate such proficiency in respect to this disease that the profession at large will willingly regard it as belonging to dermatology.

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There is little need for recapitulation. On the seal of Yale University is the inscription "Lux et Veritas." That phrase epitomizes, I believe, both our needs and our duties. And for dermatology, my prayer would be that of David: "O send out thy light and thy truth: let them lead me."

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A STUDY OF FOUR HUNDRED AND EIGHTY-FIVE CASES WITH GENITAL LESIONS *

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The conditions diagnosed in a study of 485 cases showing lesions of the genitalia clinically suspicious of venereal disease are presented in Table 1.

This series constitutes all the material of this type seen in the skin and syphilis clinic of the outpatient department of Lakeside Hospital and in private practice by me and my associate, Dr. Harold N. Cole, from Aug. 1, 1920, to Feb. 1, 1922, a period of eighteen months. The methods employed in coming to a final diagnosis will be briefly outlined.

HISTORY

The history of the case is often helpful, if accurate data can be obtained. In chancroid, the incubation period is short, as a rule less than ten days; while in syphilis the incubation period is usually from ten days to six weeks. We have found the history to be the least reliable of all clinical aids, and it should not be the sole factor in making the diagnosis.

CLINICAL APPEARANCE

The number of cases in which we see the so-called typical chancre is comparatively small. The frequency of multiple chancres, 38 per cent. in the series, the not uncommon occurrence of mixed lesions of chancre and chancroid, 3.7 per cent. in this series, and the presence of single lesions in cases of chancroid, 53 per cent. in

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our study, again make the importance of laboratory aids in diagnosis quite evident. We feel that the number of cases in which a clinical diagnosis of chancre or chancroid can be made safely is almost nil, and this method of making a diagnosis is to be discouraged. In only twenty-five cases was a diagnosis of syphilis made clinically. In these, it was impossible to follow the case to final diagnosis. None of this group received treatment by us. An efficient social service follow-up system in the Lakeside clinic made it possible to follow such a large percentage of our cases to final diagnosis.

TABLE 1.—CONDITIONS DIAGNOSED IN CASES SHOWING LESIONS OF THE GENITALIA

	Condition	No. of Cases	Percentage
1.	Chancroid	177	36.5
2.	Chancre (202 lesions)	153	31.5
3.	Chancroid and chancre (mixed)	18	3.7
4.	Chancre redux	4	0.83
5.	Secondary syphilis (moist papules)	32	6.6
6.	Herpes progenitalis	37	7.8
7.	Erosive gangrenous balanitis and vulvitis	30	6.2
8.	Nonspecific (simple) balanitis	11	2.2
9.	Folliculitis	7	1.4
10.	Ulcerating granuloma of the pudenda	8	1.65
11.	Scabies	3	0.62
12.	Tuberculous ulcer	3	0.62
13.	Epithelioma	1	0.21
14.	Kraurosis vulvae	1	0.21

LABORATORY METHODS

The laboratory methods used in this study consisted of (*a*) the dark-field illuminator for detection of *Spirochaeta pallida,* the fusiform bacillus and spirillum of Vincent; (*b*) the Wassermann test, used as a follow-up method for all cases having negative dark-field examinations and on those cases with genital lesions suspicious of secondary syphilis; and (*c*) biopsy examinations in cases diagnosed as epithelioma, tuberculous ulcer and ulcerating granuloma of the pudenda.

Dark-Field Illuminator.—Of first importance in the diagnosis of primary syphilis is the dark-field illuminator. This instrument is the most simple and accurate for the demonstration of *Spirochaeta pallida,* the procedure being no more difficult than the simple

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staining methods for the microscopic examination for the gonococcus or the tubercle bacillus. It should be in the equipment of every physician who treats venereal disease. It is lamentable that practically the only aid to the diagnosis of syphilis before the Wassermann reaction becomes positive should not be more universally used. In this series, all cases received at least one dark-field examination. In those cases not diagnosed at the first examination and which we were able to follow to ultimate diagnosis, examination by this method was made at one and two day intervals until at least four negative results were obtained.

Wassermann Reaction.—In all cases in which the diagnosis was not made by means of the dark field, the Wassermann tests on the blood of the patient were started at the end of the second week, and weekly examinations made for the first eight weeks and every two weeks thereafter. The patient was not pronounced nonsyphilitic until a negative result at the end of three months was obtained.

Biopsy.—In the few cases clinically suspicious of epithelioma and of tuberculosis, the diagnosis was confirmed by biopsy, by negative Wassermann tests and by negative dark-field examination. In all cases of ulcerating granuloma of the pudenda, biopsy examinations and microscopic smears were made.

ANALYSIS OF CASES

Syphilis.—The diagnosis of syphilis was made in 203 cases, or 42 per cent.; 178 of them being diagnosed by means of either the dark field or the Wassermann test, or both. In addition, we had twenty-five cases which were diagnosed by history and clinical evidence alone, because of the inability to follow the case through to ultimate laboratory diagnosis. In 171 cases, the diagnosis of primary lesion was made. Of this number, 98, or 57.3 per cent., had positive dark fields. Table 2 presents the results of the dark-field examinations.

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The patients in the largest group were examined between one and ten days, thirty-seven giving positive reactions and twenty-eight, negative. The fact that out of the twenty-eight negative results twenty-four cases had received previous local treatment probably accounts for the rather low percentage of positive results. It will be noted that a higher percentage of positive examinations was found in the twenty to thirty days' series than in the ten to twenty days' series. This is doubtless accounted for by the relatively small number of cases, there being but twenty-five in this group. From an analysis of these results, we are convinced that the greatest factor in preventing a diagnosis by dark field

TABLE 2.—RESULT OF DARK-FIELD EXAMINATIONS IN ONE HUNDRED AND SEVENTY-ONE CASES OF PRIMARY SYPHILIS

Duration of Chancre	Number of Cases	Dark-Field Examination		Treated Locally	Dark-Field Percentage Positive
		Positive	Negative		
1 to 10 days	67	39	28	24	58.2
10 to 20 days	48	30	18	27	62.5
20 to 30 days	25	16	9	18	64
30 to 60 days	31	13	18	22	42
Total	171	98	73	91	57.3

was local treatment of the lesions, especially with preparations of mercury. The age of the lesion did not make any appreciable difference so long as it had not been treated. In those cases in which the lesion was concealed by phimosis, examination by dark field was also very unsatisfactory. In Table 3, the location of the primary lesions in our series is shown.

It will be noted that the most common location was on the prepuce, 34 per cent., the coronal sulcus having 17.2 per cent. and the frenum 14.3 per cent. The majority of the lesions were of the papulo-erosive type. The so-called typical hunterian chancre was comparatively uncommon. Lesions of the veneer type with little or no induration were seen most frequently on the

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shaft and prepuce. In Table 4 is shown the effect of previous local treatment on the result of dark-field examinations in cases of primary syphilis.

Of a total of eighty-one chancres which had previously been treated locally, including treatment with mild antiseptics, 26 or 28.5 per cent. were positive and 65 or 71.5 per cent. were negative. It will be seen from a study of this table that the mercury preparations

TABLE 3.—LOCATION OF LESIONS IN ONE HUNDRED AND SEVENTY-ONE CASES OF PRIMARY SYPHILIS

	Condition	No. of Lesions	Percentage
1.	Prepuce	81	34
2.	Sulcus	41	17.2
3.	Frenum	34	14.3
4.	Shaft	27	11.4
5.	Glans	23	9.06
6.	Concealed (phimosis)	21	8.8
7.	Intra-urethral	3	1.3
8.	Labia majora	4	1.7
9.	Labia minora	2	0.81
10.	Vagina	1	0.42
11.	Cervix	1	0.42
	Total	238	

TABLE 4.—EFFECT OF LOCAL TREATMENT ON THE DARK-FIELD EXAMINATION OF EIGHTY-ONE CHANCRES

Drug Used	Number of Cases	Dark-Field Positive	Dark-Field Negative	Dark-Field Negative Percentage
Mercury preparations	17	1	16	94.4
Tincture of iodin	5	4	1	20
Copper sulphate	4	0	4	100
Hydrogen peroxid	10	8	2	20
Actual cautery	7	5	2	30
Doubtful	36	5	31	86
Compound solution of cresol	2	0	2	100
Total	81	23	58	

nearly always inhibit the possibility of demonstrating *Spirochaeta pallida,* there being 94.4 per cent. negative results. In only one instance out of seventeen was the dark field positive after the use of mercury preparations locally. Copper sulphate used in four cases and compound solution of cresol in two inhibited the dark field in each instance, indicating that as spirocheticides they are very effectual. The actual cautery failed to

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prevent the demonstration of the organism in only two cases out of seven. Hydrogen peroxid is also of practically no hindrance in the demonstration, eight tests out of ten being positive. In thirty-six cases, the drug used was unknown, it being a white powder or salve procured from the drug store. In the majority of cases, it was probably calomel. There were thirty-one failures to demonstrate the organism in this group.

In eighty cases of chancre, there was no history of previous local therapy. The dark field was positive in seventy-three instances, or 81 per cent. It is seen, therefore, that in the locally treated group only 28.5 per cent. were diagnosed by dark field, while in the untreated series 81 per cent. were positive by this method.

The comparative infrequency of the diagnosis of primary syphilis in the female is striking in our series. Out of 171 primary infections, there were only eight cases of chancre in women, of which six were diagnosed by the dark field. This, perhaps, is explained by the occurrence of the primary lesion in the vagina or on the cervix in many cases, where it is not discovered by the patient or physician. The majority of cases of secondary eruption in women are without a history of a sore having been noticed.

In our series of primary syphilis, there are four cases of reinfection. In all cases, the previous diagnosis had been made by the dark field, and the Wassermann reactions were negative. In each instance, the second chancre was in a new location. The dark-field examination was positive and Wassermann reaction negative in each instance.

A diagnosis of secondary syphilis was made in thirty-two cases. In each instance, lesions of the moist, papular type, suspicious of syphilis, were present, without evident secondary skin eruptions. The dark-field examination was positive in all.

Chancroids.—Because of the difficulty in demonstrating the Ducrey bacillus by either cultures or

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smears, and because of the difficulty of controlling ambulatory cases after autoinoculation, the diagnosis of this condition was made clinically in each instance. There are 195 cases in this series, 179 in males and sixteen in females. In eighteen cases, or 0.87 per cent., the disease was associated with chancre. This leaves 177 cases with a diagnosis of chancroid alone. Of this number eighty-three, or 46.9 per cent., were multiple. One hundred and ten cases, or 62.1 per cent., showed definite, painful inguinal adenitis. Of these, fifty-four cases went on to suppuration, while fifty-six were nonsuppurating. The plan of hospitalizing the patients in as many instances as possible, with rest in bed and ice packs locally, we feel, is responsible for the low percentage of nonsuppurating cases. The fact that nearly one half of the series showed on examination single lesions is noteworthy.

Herpes Progenitalis.—There were thirty-seven cases of genital herpes, or 7.8 per cent. of the total series. There were twenty-eight cases in males and nine in females. In eleven cases, there was a history of previous venereal disease. Seven patients had had gonorrhea; three had syphilis and one chancroid. In twenty-two cases, there was a history of one or more previous attacks. Our series with 75 per cent. in males and 25 per cent. in females agrees with most authorities that the condition is more common in males. When abraded or secondary infection is present, the process may be confused with chancroid, or possibly an early chancre. The absence of positive dark-field findings and follow-up Wassermann tests, associated with a sensation of burning and itching, with a history usually of previous attacks and the lack of induration and inguinal adenitis, makes the diagnosis usually not difficult.

Erosive Gangrenous Balanitis and Vulvitis.—There were thirty cases, or 6.2 per cent. of the total series. It is my opinion that this condition is, perhaps, much

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more common than is generally supposed. In each instance, diagnosis was made by demonstrating the fusiform bacillus and spirillum of Vincent in dark-field preparations. Most cases of so-called phagadenic chancroid, we believe to be due to this organism. In our study of 485 cases, there were no cases of phagadena. In all cases suggesting this, diagnosis of erosive gangrenous balanitis was made by the dark field. Early recognition of this disease should be emphasized; for once the process has gone beyond the stage of superficial erosion, it is difficult to prevent extensive destruction. In the first few days of the disease, the patient usually complains of a burning irritation of the glans and foreskin. The case at this stage presents a rather abundant, greenish, purulent discharge, which, when removed, reveals a very superficial erosion of the epidermis on a red, inflamed surface. Examination of the discharge with the dark-field illuminator reveals many of the organisms described above. To the practiced eye, there is no difficulty in differentiating the large, irregular, unequal, waved, rapidly moving spirillum from the shorter, delicate, slowly moving *Spirochaeta pallida* with its spirals of equal wave length. We have at times found the two organisms in the same patient and on the same lesions. A diagnosis of both erosive gangrenous balanitis and chancre from a single dark-field preparation should be most carefully made because of the polymorphous character of the spirillum of Vincent. In this series, five cases were in females and twenty-five in males. In only fourteen of the thirty cases had there been an exposure within three weeks. The disease is not always of venereal origin. In a few cases, the possibility of oral etiology was well established. The majority were in patients with long foreskins, and uncleanliness doubtless was a contributory factor in many instances.

Nonspecific Balanitis.—Eleven cases, or 2.2 per cent. of the series, were diagnosed as simple balanitis. Dif-

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ferential diagnosis from erosive gangrenous balanitis was most necessary. Dark-field examination with follow-up Wassermann tests in some cases is sufficient to clear up the diagnosis. The use of strong antiseptic preparations for prophylaxis is the most common cause of this condition. Irritating secretions in cases of acute gonorrhea and, in some instances, uncleanliness, are responsible.

Folliculitis.—Seven cases, or 1.4 per cent., were diagnosed as folliculitis. Lesions are usually on the shaft near the base of the penis and occasionally develop into furuncles.

Ulcerating Granuloma of the Pudenda.—There were eight cases representing 1.65 per cent. of the series. In all the cases, biopsy examinations and microscopic smears were made in addition to dark-field and Wassermann tests. All the cases but one were in women. Examination for the Leishman-Donovan organism was in only three cases satisfactory, and we arrived at the diagnosis largely by clinical means. Biopsy examinations reveal pathologic conditions similar to those of other granulomatous processes. There is marked chronic inflammation with elongation of the papillae and interpapillary processes, usually. There is round-cell infiltration in the upper corium. The absence of giant cells and caseation helps to rule out tuberculosis, and malignancy is ruled out by the pathology also. The blocking of the draining lymph channels may produce a pseudo-elephantiasis of the vulva, as seen in three of our cases. The Wassermann test may be positive (six cases in this series); but in our experience the disease is not influenced in the least by antisyphilitic therapy. The disease is most common in the negro (seven out of eight cases in this series). All of our cases were cured with antimony and potassium tartrate (tartar emetic), reacting to this remedy only. The intravenous method was used. One cubic centimeter of a 1 per cent. solution was given as the initial

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dose. This was increased 1 c.c. each dose until the patient received 12 c.c. as a dose. Injections were given twice each week until an average of about twelve or fifteen treatments were given. Some of our patients received as high as thirty-five injections without bad effects. There have been no recurrences to our knowledge. The diagnosis of ulcerating granuloma of the pudenda we feel should be considered in all cases, especially in colored females from Southern states, with chronic, ulcerating lesions of the genitalia.

Scabies.—There were only five cases of scabies examined by the dark field. In these cases, the presence of lesions only on the genitals made them clinically suspicious of chancre. The ultimate appearance of typical lesions on the classic areas of the body, with negative laboratory findings of syphilis, cleared up the diagnosis.

Tuberculosis.—In three cases, a history of ulcer of several months' duration, with negative laboratory findings and a pathologic picture most suggestive of tuberculosis, determined the diagnosis.

Epithelioma.—We had one case of several months' duration in an elderly man. Laboratory findings of venereal disease were negative. Biopsy examination revealed squamous-cell carcinoma.

Kraurosis Vulvae.—One case was seen. The condition is uncommon. The presence of superficial erosion suggested the possibility of erosive gangrenous vulvitis. The long duration, associated with pruritus and itching, with atrophy and almost complete disappearance of the labia, and with a chronic, irritating discharge from the cervix, in addition to negative laboratory and physical findings for venereal disease, made the diagnosis of kraurosis vulvae most plausible.

SUMMARY

1. In a study of 485 genital lesions coming up for diagnosis, we found syphilis in 203 cases, or 42 per cent. This frequency is rather startling and is a

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reminder of how careful we must be of ruling out this disease in all genital lesions. We are convinced that too often the patient with a genital lesion is discharged as being free from syphilis after one or more cursory examinations—the undiagnosed syphilis revealing itself later.

2. Chancroids were seen 177 times, or in 36.5 per cent., and in eighteen cases there was a mixture of chancroids and syphilis.

3. The occurrence of four cases of reinfection with syphilis in our series, all with patients whose dark-field examination was positive and Wassermann reaction negative at the time of the first infection, emphasizes the importance of the early diagnosis of the disease, such cases apparently reacting better to treatment. It also emphasizes the value of our modern methods of treatment when properly and consistently carried out.

4. Ulcerating granuloma of the pudenda was encountered eight times in our series of cases, all but one of the cases being seen in negroes. This rare disease of the tropics is apparently becoming more common in our part of the world, or we are diagnosing a disease which in the past has been overlooked. In our experience, tartar emetic was a specific, and the sole specific, for the trouble.

5. Erosive gangrenous balanitis and vulvitis was seen in thirty patients, mostly males, and is best diagnosed by the dark-field illuminator. It is important that the disease be recognized at its inception, and that specific treatment be begun before the destructive results of the disease have set in.

6. The clinical diagnosis of primary syphilis is open to many serious objections and should not supplant the use of laboratory methods. The dark-field examination is preferable to the Wassermann test in the early recognition of primary lesions. All cases not diagnosed by dark field should be followed by Wassermann

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examinations on the blood at regular intervals for at least three months.

7. It is important that physicians realize that the chances of making an early diagnosis of syphilis are greatly diminished, about three to one in our series, if local antiseptics are used on genital lesions before dark-field examinations are made. In seventeen cases in which we were positive that some form of mercury had been used on the lesions, we were able to make an early dark-field diagnosis in only one case.

8. It may be interesting to note that among 171 primary lesions, only eight chancres were observed in females—six of them being diagnosed by the dark-field illuminator. This may be due to the fact that the female notes no evidence of the disease in a large majority of the cases before secondary symptoms intervene; or due to the examining physician's failing to find the primary seat of invasion in the vagina or on the cervix.

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THE KAHN PRECIPITATION TEST IN THE DIAGNOSIS OF SYPHILIS

A PRELIMINARY STUDY *

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Recently Kahn [1] has proposed for the serologic diagnosis of syphilis a precipitation reaction in which he utilizes, as antigens, alcoholic extracts of heart muscle, with and without the addition of cholesterin. The clinical application of this reaction, in 350 unselected cases entering the service of dermatology and syphilology of the University Hospital, Ann Arbor, forms the basis of this study.

Since the introduction of a practical complement fixation test by Wassermann, Neisser and Bruck,[2] in 1906, serologists and clinicians have directed their efforts toward modifications of that procedure in the hope of developing a laboratory method that will retain the obvious advantages of the Wassermann test and eliminate the well-known difficulties encountered in its performance.

The precision and care with which the various ingredients entering into complement fixation have to

* Studies and contributions of the Department of Dermatology and Syphilology of the University of Michigan, service of Dr. Udo J. Wile.

1. Kahn, R. L.: A Simple Quantitative Precipitation Reaction for Syphilis. Preliminary Communication, Arch. Dermat. & Syph. **5**: 570 (May) 1922; Second Communication, ibid., **5**: 734 (June) 1922; Third Communication, ibid., to be published; Effect of Dilution on Precipitation Reaction for Syphilis Proposed by Author, Proc. Soc. Exper. Biol. & Med. **19**: 131 (March 15) 1922; Relation between Serum and Antigen in Precipitation Reaction for Syphilis Proposed by Author, ibid. **19**: 132 (March 15) 1922.

2. Wassermann, Neisser and Bruck: Eine serodiagnostische Reaktion bei Syphilis, Deutsch. med. Wchnschr., 1906, p. 745.

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be titrated are well known. The main difficulty, however, is that, after these titrations have been properly carried out, there still remain numerous variants which are potential sources of error. The most common error arises from the fact that the important reagent, namely, complement, tends to deteriorate with relative rapidity. Since the test is based on the disappearance of complement activity, it is evident that the possibility of mistaking complement deterioration for specific action is always present. A second frequent source of error is found in the occasional partially anticomplementary action of the serum. In such cases, the serum will absorb some complement without antigen. Assuming that a strongly anticomplementary serum is readily detectable by means of proper controls, partially anticomplementary serums are not so easily controlled, and therefore may lead to false positive results. Finally, many serums contain natural hemolysin, which would obviously lead to false negative results.

These, and many other technical difficulties undoubtedly explain why, in spite of the fact that the Wassermann reaction has now been in use more than fifteen years, it is not, as yet, wholly dependable.

In order to overcome the numerous difficulties encountered in the performance of this test and in the interpretation of the results, various biochemical procedures have been introduced in recent years. Among these, several precipitation reactions have been advanced, which gave promise of simplification and general usage.

These reactions have been favorably commented on in Germany, but, judging from the paucity of the literature, have attracted little attention in England and in this country. The first precipitation reactions of practical application were those described by Meinicke [3] in

3. Meinicke, E.: Ueber eine neue Methodik der serologischen Luesdiagnostik, Berl. klin. Wchnschr. **54**: 613, 1917; Ueber Theorie und Methodik der serologischen Luesdiagnostik, ibid., 1918, No. 4, p. 83; Zur Methodik der serologischen Luesdiagnostik, München. med. Wchnschr. **65**: 1379, 1918; Ueber die dritte Modifikation meiner Luesreaktion, ibid., 1919, No. 33, p. 932.

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1917, and by Sachs and Georgi[4] in 1918. The main difficulty with these reactions lies in the fact that the end-results are read after forty-eight hours' incubation; at the end of such time, serums frequently show sufficient contamination to lead to false interpretations.

For the foregoing reason, Dreyer and Ward[5] in England, and Kahn in this country, came to the conclusion that neither of these two reactions can be utilized as a practical diagnostic test for syphilis.

Dreyer and Ward[5] introduced a precipitation reaction which requires such elaborate care in preparation and dilution of its antigens, and so many tubes for each test (nine), that it offers no practical advantages over the Wassermann technic.

A still more recent precipitation test has been proposed by Wang.[6] This test embodies the use of an antigen, which shows slight turbidity on diluting with physiologic sodium chlorid solution, thus obviously rendering difficult the reading of sharp end-results. In our opinion, for a practical precipitation reaction, both the antigen and the serum should be absolutely clear. Under such conditions only can the formation of a precipitate, after mixing the two substances, be presumed to be specific.

The precipitation reaction employed in this study not only meets the requirement with regard to the employment of a clear antigenic solution, but, in addition, possesses other advantages which we believe will meet with favor. For example, the test can be carried out with relative simplicity, and the final precipitate is readily visible to the naked eye. Also, in strongly positive serums, spontaneous flocculation occurs, enabling interpretation as soon as the reagents are thoroughly mixed.

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4. Sachs, H., and Georgi, W.: Zur Serodiagnostik der Syphilis mittels Ausflockung durch cholesterinierte Extrakte, Med. Klin., 1918, No. 33, p. 805.

5. Dreyer, Georges, and Ward, H. K.: A Simple Quantitative Serum Reaction for the diagnosis of Syphilis, Lancet 1: 956 (May 7) 1921.

6. Wang, C. Y.: A Precipitation Test for Syphilis, Lancet 1: 274, 276 (Feb. 11) 1922.

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The Kahn reaction further distinguishes itself from other precipitation reactions by these salient features:

1. The serum is employed in an undiluted form, it having been shown by Kahn that diluting the serum with salt solution delays the rapidity of the reaction.

2. The antigen is prepared so as to contain a high content of antigenic material. This is attained by using an alcoholic extract of dried heart muscle, which has been previously extracted with ether, thus removing fat and other nonspecific substances.

3. The antigen is diluted for the test with approximately the smallest amount of physiologic sodium chlorid solution which will hold it in solution, rendering it thereby susceptible to precipitation when mixed with positive serum.

4. The antigen and serum are employed in that relationship which will, in the author's opinion, result in maximum precipitation.

These features give this reaction such a high degree of sensitiveness that the strongly positive serums react spontaneously in most cases.

THE METHOD

Preparation of the Antigens.—Fresh beef heart is freed from fat, fiber and blood vessels, and passed several times through a meat chopper. It is then spread in a thin layer on a porcelain platter and dried by means of a revolving fan. The dried material is broken into small particles and passed three times through a coffee grinder. Fifty grams of the dried heart muscle is then placed in a 500 c.c. Erlenmeyer flask; sufficient ether is added to cover the dried material with an inch of fluid, and it is placed in the icebox. After twenty-four hours' extraction, the supernatant ether is quite yellowish; it is then poured off and replaced with fresh ether. This is repeated daily for three days. On the fourth day, the supernatant ether is water clear. The ether is then filtered off and the ground muscle spread on paper and dried at room temperature until no odor of ether is detectable. This requires several hours' drying.

To 20 gm. of this material, 100 c.c. of absolute alcohol is added, and the whole extracted for nine days in the icebox and one day at room temperature. After this period, the alcoholic extract is filtered off. A total of 70 c.c. of alcoholic antigen is usually thus obtained. To half this quantity is

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added 140 mg. of cholesterin, which is dissolved by rotating the flask. The other 35 c.c. is used as a control noncholesterinized antigen.

Dilution of Antigen for the Tests.—The antigens thus prepared are diluted for the tests as follows: From 0.5 to 1 c.c. of the cholesterinized antigen is pipetted into an agglutination tube, inner diameter about three-eighths inch (10.5 mm.), depending on the amount needed for the group of tests. Three times the amount of physiologic sodium chlorid solution (0.85 per cent.) is then measured into a 10 c.c. cylinder. This solution is rapidly poured into the agglutination tube and promptly inverted back and forth. The noncholesterinized antigen is diluted in a similar manner except that two parts of physiologic sodium chlorid solution to one part of antigen are employed. Both of these mixtures appear clear and opalescent. They are used in most cases within an hour after dilution. On several occasions, the antigens were used several days after mixing, having been kept in the incubator during that time. However, this older antigen did not seem to be as sensitive as that used shortly after the addition of the physiologic sodium chlorid solution. It is, therefore, desirable to use fresh dilutions of the antigen for each day's tests.

The serum was separated by rapid centrifugation, and inactivated for one-half hour in the water bath at 56 C. It was then ready for use.

Performance of the Test.—Three-tenths cubic centimeter of serum is measured into each of two agglutination tubes. To the first tube 0.05 c.c. of the diluted cholesterinized antigen is added, and the same quantity of the noncholesterinized mixture is added to the other. The remainder of the serum is carried along with the procedure as a control. The rack of tubes is vigorously shaken for three minutes. At this point, strongly reacting serums show definite precipitation, particularly with the cholesterinized antigen. These are recorded as spontaneous precipitations.

The rack is then placed in the incubator (37.5 C.) and permitted to remain overnight, in order to bring out precipitation in the relatively weaker serums. The results are read the next morning without again shaking the rack. The precipitates, being suspended in the clear serums, can be seen with comparative ease.

The results are recorded in accordance with the following scale:

1. A precipitate, consisting of one or more large clumps = ++++.
2. A large flocculent precipitate = +++.
3. Moderate-size flocculi or granules = ++.
4. Small-size flocculi or granules = +.
5. Fine flocculi or granules = ±.
6. Negative precipitation = —.

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When working with strongly positive serums, it was observed that a precipitation ring frequently formed at the point of juncture of the serum and diluted antigen, a few minutes after adding the latter. This suggested the possibility of developing a ring modification with this precipitation reaction. A series of experiments was then performed in which, after the addition of the antigen to the serums, the mixture was placed in the incubator without shaking the tubes. The diluted antigen, being lighter than the serum, formed a layer over the latter, which was readily visible. Incubation intensified this reaction; but it was noted that not infrequently many moderately positive serums reacted negatively with this procedure, and positively when the regular procedure was employed. This fact would seem to enhance the importance of thoroughly mixing the serum and antigen. Vigorous shaking apparently brings the combining elements of the serum and antigen into closer contact, thereby hastening the reaction.

Clinical Material.—The cases studied can be classified as shown in Table 1.

The cases other than syphilis included, for the most part, the more common conditions seen in a dermatologic dispensary, such as the infectious granulomas, carcinoma, papulosquamous conditions, eczema, acne vulgaris and allied dermatoses.

Comparison with Wassermann Reaction.—Aside from running a precipitation reaction on each serum, a quantity of blood was submitted from each patient to the Wassermann laboratories of the state psychopathic hospital at Ann Arbor, and to the state department of health at Lansing. It seemed desirable not only to investigate the value of this precipitation test in the diagnosis of syphilis, but also to learn to what extent it compares with the Wassermann test as carried out in two different standard laboratories.

It should be stated that there is an important technical difference between these two Wassermann tests;

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in the state laboratory the period of complement fixation with the cholesterinized antigen is one hour in the icebox,[7] while the complement fixation period with a similar antigen at the psychopathic hospital is twelve hours in the icebox.

The accompanying tables show the results of the Kahn test, as compared with two standard Wassermann tests, in 350 cases.

TABLE 1.—CLASSIFICATION OF CASES

Condition	Number of Cases
1. Primary syphilis	12
2. Secondary syphilis	15
3. Tertiary syphilis, excluding cerebrospinal	19
4. Cerebrospinal syphilis	52
5. Congenital syphilis	15
6. Latent syphilis	80
7. Other than syphilis	157
Total	350

TABLE 2.—PRIMARY SYPHILIS

		Wassermann Reaction		
Case	Kahn Reaction	12-Hour Fixation Icebox	1-Hour Fixation Icebox	Treatment
1	++++ (spontaneous reaction)	++++	++++	None
2	++++ (spontaneous reaction)	++++	++++	None
3	++++ (spontaneous reaction)	++++	++++	None
4	++++ (spontaneous reaction)	++++	++++	None
5	++++ (spontaneous reaction)	++++	++++	None
6	++++ (spontaneous reaction)	++++	++++	Indifferent
7	++++ (spontaneous reaction)	++++	+	Indifferent
8	++	+++	++	Indifferent
9	++	++	—	Thorough
10	++	—	—	Thorough
11	—	—	—	Thorough
12	—	—	—	None

Primary Syphilis.—It will be seen from Table 2 that more than 50 per cent. of the cases examined reacted spontaneously. Also, there is agreement in the three reactions in 66⅔ per cent. of the twelve cases studied. The remaining 33⅓ per cent. show a sensitiveness in favor of the Kahn reaction.

7. Kahn, R. L.: Optimum Conditions of Fixation of Complement in the Wassermann Test, Arch. Dermat. & Syph. 4: 358 (Sept.) 1921.

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The serum in Case 10 was taken shortly after an intensive course of therapy, and followed a ++++ Wassermann reaction before the inauguration of treatment. The lesion was rapidly involuting when first seen. This serum is interesting in that, notwithstanding the institution of treatment, it is still ++ positive to the Kahn reaction, while negative to the Wassermann tests.

TABLE 3.—SECONDARY SYPHILIS

		Wassermann Reaction		
		12-Hour Fixation	1-Hour Fixation	
Case	Kahn Reaction	Icebox	Icebox	Treatment
1	++++ (spontaneous reaction)	++++	++++	None
2	++++ (spontaneous reaction)	++++	++++	None
3	++++ (spontaneous reaction)	++++	++++	None
4	++++ (spontaneous reaction)	++++	++++	None
5	++++ (spontaneous reaction)	++++	++++	None
6	++++ (spontaneous reaction)	++++	++++	None
7	++++ (spontaneous reaction)	++++	++++	Indifferent
8	++++ (spontaneous reaction)	++++	++++	Indifferent
9	++++ (spontaneous reaction)	++++	++	None
10	++++	++++	++	Indifferent
11	+++	++++	—	Thorough
12	++	++++	++	None
13	++	++++	+	Thorough
14	++	++	+	Indifferent
15	++	—	—	Thorough

Case 9, a chancre of the lip, following intensive treatment, is positive to the precipitation and long icebox fixation reactions, but negative in the shorter incubation Wassermann. This patient still has residual induration six months after infection.

Secondary Syphilis.—In this group, the greatest proportion of spontaneous reactions are found. The three tests show agreement in eight of the fifteen serums examined. In the other seven cases, the Kahn reaction compares favorably in point of sensitiveness.

In Case 15, in which the test is still positive with the precipitation reaction, but negative with the Wasser-

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mann tests, the patient had just completed an intensive course of arsphenamin.

Tertiary Syphilis.—In late cutaneous syphilis, it will be seen that the Kahn reaction is not as sensitive as the Wassermann with the longer period of icebox fixation. It is, however, more sensitive than the Wassermann reaction with the short incubation period. In this

TABLE 4.—TERTIARY SYPHILIS (EXCLUDING CEREBROSPINAL)

Case	Kahn Reaction	Wassermann Reaction: 12-Hour Fixation Icebox	Wassermann Reaction: 1-Hour Fixation Icebox	Treatment
		Cutaneous		
1	++++ (spontaneous reaction)	++++	++++	None
2	++++ (spontaneous reaction)	+++	++++	None
3	++++ (spontaneous reaction)	++++	++++	Indifferent
4	++++ (spontaneous reaction)	++++	+++	Indifferent
5	++++	++++	+	Indifferent
6	+++	++++	+	Indifferent
7	++	++++	+++	Indifferent
8	++	++++	++	Indifferent
9	—	—	—	Indifferent
		Osseous System		
1	++++ (spontaneous reaction)	++++	++++	None
2	++++ (spontaneous reaction)	++++	++	None
3	+++ (spontaneous reaction)	+++	±	Indifferent
4	+	—	—	None
5	—	—	+	Indifferent
6	—	—	—	None
		Visceral		
1	++++ (spontaneous reaction)	++++	++++	None
2	++++	++++	+	Thorough
3	++++	+++	++	Thorough
4	++++	++	++	None

connection, it should be noted that the latter Wassermann reaction is weaker, notwithstanding that this group of cases had been indifferently treated.

In the serums examined from patients with late bone and joint involvement, the Kahn reaction again compares very favorably with the two Wassermann reactions.

Case 4 is one of septal perforation. One year ago, this patient had a ++++ Wassermann reaction.

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There has been no therapy in the interim, and at the present time the precipitation test is weakly positive, with both Wassermann reactions negative.

Case 5, an old gummatous periostitis, was indifferently treated. This patient's serum, however, is negative with the Kahn test, as well as with the Wassermann

TABLE 5.—CEREBROSPINAL SYPHILIS *

Case	Kahn Reaction	Wassermann Reaction: 12-Hour Fixation Icebox	Wassermann Reaction: 1-Hour Fixation Icebox	Treatment
		Diffuse Type		
1	++++ (spontaneous reaction)	++++	++	Thorough
2	++++	++	++++	Indifferent
3	+++	++++	+++	Indifferent
4	+++	++++	++	Indifferent
5	+++	++++	++	None
6	+++	++++	+	Thorough
7	+++	+++	—	Indifferent
8	+++	±	+	Thorough
9	++	++++	++++	Thorough
10	++	++++	—	Thorough
11	++	++++	++	Thorough
12	++	++	—	Indifferent
13	++	—	±	Thorough
		Tabes Dorsalis		
1	++++ (spontaneous reaction)	++++	+++	None
2	++++ (spontaneous reaction)	++++	++	None
3	++++ (Spontaneous reaction)	++++	++	Thorough
4	+++ (Spontaneous reaction)	+++	+	Thorough
5	++++	++	++	Thorough
6	++++	+	—	Thorough
7	+++	++++	++	Indifferent
8	++	++	+	Indifferent
9	++	+	—	Thorough
10	—	++	—	Thorough
		General Paresis		
1	++++	++++	+	Thorough
2	+++	++++	++	Indifferent
3	+++	++++	+	Thorough
4	++	++++	+	Thorough
5	++	++++	+	Thorough
6	+	++	—	Thorough

* This group, which numbered fifty-two cases, completely agreed in the three reactions in 45 per cent.

test of the long incubation period, and positive with the Wassermann reaction, short fixation period. At the time the blood was drawn, the patient had a temperature elevation of 4.5 degrees from an undetermined cause.

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Case 6 is an old specific perforation of the hard palate. Here the Kahn test does not appear more sensitive than the Wassermann, all three being negative.

In the few cases of visceral involvement studied, the Kahn test, as may be seen from the table, was slightly more sensitive than either Wassermann test.

Cerebrospinal Syphilis.—Of the fifty-two cases studied, twelve, or 23.07 per cent., showed spontaneous precipitation. Only five of the spontaneous reactions are presented, as the other seven showed complete

TABLE 6.—CONGENITAL SYPHILIS

		Wassermann Reaction		
Case	Kahn Reaction	12-Hour Fixation Icebox	1-Hour Fixation Icebox	Treatment
1	++++ (Spontaneous reaction)	++++	++++	None
2	++++ (Spontaneous reaction)	++++	++++	None
3	++++ (Spontaneous reaction)	++++	++++	Indifferent
4	++++ (Spontaneous reaction)	++++	++++	Indifferent
5	++++ (Spontaneous reaction)	++++	++++	Indifferent
6	++++ (Spontaneous reaction)	++++	—	Thorough
7	++++	++++	+++	Thorough
8	++++	++++	++	Thorough
9	++++	++++	++	Indifferent
10	+++	++++	++	Thorough
11	+++	++++	++	Thorough
12	++	++++	+	Thorough
13	++	—	—	None
14	+	—	—	Thorough
15	+	—	—	Thorough

agreement in the three tests. Table 5 presents only the variations, from which it will be seen that the Kahn reaction again compares favorably with the more sensitive Wassermann test.

Cases 8 and 13 of the diffuse cerebrospinal syphilis, both of which were thoroughly treated, nevertheless gave a stronger reaction with the simple precipitation method than with either Wassermann test.

In tabes dorsalis, similar favorable comparison will be seen, although a negative reaction was obtained in Case 10, in which one Wassermann was also negative.

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In the general paresis, the precipitation test is slightly less sensitive in comparison with the long icebox fixation Wassermann reaction, but markedly more sensitive than the short icebox fixation Wassermann test.

Congenital Syphilis.—From Table 6, it will be observed that the Kahn reaction is slightly more sensitive than either Wassermann test in congenital syphilis.

Case 13 is that of a girl 16 years of age, who shows unquestionable stigmas, but has been repeatedly negative to many Wassermann tests. The patient's serum,

TABLE 7.—LATENT SYPHILIS *

Case	Kahn Reaction	Wassermann Reaction: 12-Hour Fixation Icebox	Wassermann Reaction: 1-Hour Fixation Icebox	Treatment
1	+++	++++	—	Thorough
2	+++	++	—	None
3	+++	+++	±	Indifferent
4	+++	+	+	Indifferent
5	+++	±	±	Indifferent
6	++	++++	—	Indifferent
7	++	+++	±	Thorough
8	++	++	—	Thorough
9	++	±	—	None
10	++	±	—	Thorough
11	++	—	—	Thorough
12	++	++	±	Thorough
13	++	++++	±	Indifferent
14	++	±	±	Thorough
15	+	+++	—	Thorough
16	+	—	—	Thorough
17	+	—	—	Thorough
18	+	++++	—	Indifferent
19	—	++	±	Thorough

* This group, which numbered eighty cases, completely agreed in 60 per cent. and practically agreed in 16.3 per cent. Only the divergences are shown in this table.

on two examinations, gave a positive result with the precipitation test, being negative with the Wassermann reaction.

Cases 14 and 15 show a sensitiveness in favor of the Kahn reaction. They are both cases of congenital syphilis in children who had been intensively treated for one year.

Latent Syphilis.—Of the eighty cases studied, seventeen, or 21.2 per cent., gave spontaneous reactions, none of which are shown in Table 7.

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The greater sensitiveness of the precipitation reaction, as compared to both Wassermann reactions, is met in this group. Cases 11, 16 and 17 would have been passed as cured, or nonsyphilitic, on the basis of the two Wassermann tests, but were detected by the precipitation reaction. Cases 2, 8, 9, 10, 15 and 18 would have been interpreted as negative, or cured, by the shorter incubation Wassermann reaction, weakly positive by the longer fixation, and positive in each case with the precipitation reaction.

The sole exception is Case 19, in which a thoroughly treated patient reacted negatively with the precipitation reaction, positively with one Wassermann reaction, and doubtfully positive with the second Wassermann.

TABLE 8.—NONSYPHILITIC CONTROL SERUMS *

Case	Kahn Reaction	Wassermann Reaction: 12-Hour Fixation Icebox	Wassermann Reaction: 1-Hour Fixation Icebox	Diagnosis
1	++	—	—	Acne vulgaris, sebaceous cysts
2	+	—	—	Variola
3	+	—	—	Pyodermia, diabetes mellitus

* Of the total number of nonsyphilitic control serums examined, there was complete agreement in 154. The three variants are shown.

It may be noted that, in a few of the cases in this table, the longer fixation Wassermann test shows a slightly stronger degree of positiveness than the precipitation test.

In this important group of asymptomatic cases, the precipitation reaction is apparently more dependable as a diagnostic procedure than the Wassermann test.

Nonsyphilitic Control Serums.—Of 157 dermatologic cases employed as controls, 154 were uniformly negative. As shown in Table 8, three cases were negative with both Wassermann reactions. Case 1 showed a ++ Kahn reaction and Cases 2 and 3, a +. These were, respectively, cases of acne, variola and diabetes. We were unable to explain these comparatively weak positive findings in apparently negative cases.

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CONCLUSIONS

1. The clinical application of the Kahn precipitation test compares favorably in sensitiveness with the standard Wassermann reaction.

2. It has obvious great advantages over the Wassermann reaction in: (1) simplicity of procedure, (2) rapidity of reading, and (3) reduction of the sources of error through elimination of a hemolytic system.

3. Its obvious advantages over other precipitation reactions lie in the visibility of the precipitate to the naked eye, and the frequent spontaneous reactions with strongly positive serums.

4. Further confirmatory tests, demonstrating parallelism with the Wassermann reaction, may well lead to the eventual abandonment of the latter in favor of the simpler precipitation procedure.

5. As a last advantage, a test embodying only one reagent plus a serum offers a greater possibility of standardization.

We are indebted to Dr. Kahn for the use of the manuscript of his third communication (mentioned in Footnote 1) previous to publication.

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STUDIES IN ASYMPTOMATIC NEUROSYPHILIS

IV. THE APPARENT RÔLE OF IMMUNITY IN THE GENESIS OF NEUROSYPHILIS *

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The operation of immune reactions in syphilis has long been suspected, speculation centering for the most part on the mechanism involved in various clinical phenomena associated with the course of the disease. The laws formulated by Colles and Profeta were early pronouncements of such a conception, and the refractoriness of infected individuals to reinoculation still forms one of the bases on which modern theories are founded. The periodicity with which clinical manifestations make their appearance from the beginning to the end of the disease, and the regular manner in which the earlier lesions particularly undergo spontaneous involution, suggest that the latter are outward expressions of a mechanism which spasmodically protects the individual from the infection, but which is unable in the vast majority of cases completely to eradicate it. Related phenomena associated with the ability of the organisms to produce increasingly harmful results are observed in the later manifestations of the disease, as witnessed by the greater degree of tissue reaction in response to insignificant toxic stimulation. The former phenomena point to a protective immunity, and the latter to a sensitizing (immunity) reaction.

IMMUNITY IN SYPHILIS FROM CLINICAL AND EXPERIMENTAL STANDPOINTS

The manner in which these mechanisms operate is as yet little understood. Immunologic studies of the

* From the Syphilis Department of the Medical Clinic, Johns Hopkins Hospital.
* This investigation has been aided by grants from the United States Interdepartmental Social Hygiene Board, and the American Social Hygiene Association.

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body fluids have thrown little if any light on the problem, although much work has been expended along this line. Circulating antibodies directed against the treponemes apparently are not present in the blood stream; at least, we have no direct evidence that such neutralizing substances are produced in sufficient amounts to be effective. Indirectly, superinoculation experiments suggest this type of immunity, but a causal relationship still remains to be demonstrated. Avirulence of culture pallida and group reactions with nonspecific treponemes and spirochetes add difficulties to this line of research.[1]

The limitation of justifiable experimentation in human subjects practically closes this field of investigation, so that the pursuit of data in the living subject is narrowed to the field of animal syphilis, more particularly rabbit syphilis. In this animal, syphilis is manifested by local and by metastatic lesions which conform somewhat remotely to types observed in human syphilis, but differ from the latter in intensity of reaction, variety, and in the order of their appearance. In other respects, however, the course of the disease and the maintenance of the infection present striking points of similarity.

In this country, at least, most of the data bearing on immunity derived from this source have resulted from the investigations and conceptions of Brown and Pearce. From the enormous amount of data which they have accumulated, two groups of observations stand out prominently in this connection, on account of the light which they throw on the mechanism of immunity.[2] The groups of phenomena have the force

1. Zinsser, Hans, and Hopkins, J. G.: Antibody Formation Against Treponema Pallidum Agglutination, J. Exper. Med. **21**: 576, 1915. Zinsser, Hans; Hopkins, J. G., and McBurney, M.: The Difference in Behavior in Immune Serum Between Cultivated Nonvirulent Treponema Pallidum and Virulent Treponemata from Lesions, J. Exper. Med. **23**: 341 (March 1916. Kolmer, J. A., and Broadwell, S.: The Relation of Luetin Skin Reaction to Immunity in Syphilis (Including Treponemecidal Action of Human Serum in Syphilis), J. Immunol. **1**: 429 (Aug.) 1916.

2. Brown, W. H., and Pearce, L.: The Resistance (or Immunity) Developed by the Reaction to Syphilitic Infection, Arch. Dermat. & Syph. **2**: 675 (Dec.) 1920; Experimental Production of Clinical Types of Syphilis in the Rabbit, ibid. **3**: 254 (March) 1921.

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of laws in that they occur regularly and are controllable within the limits of experimentation. I refer to the phenomena described as the "law of progression" and the "law of inverse proportions." According to the former, various tissue groups are not equally susceptible and reactive to syphilitic infection, so that in the generalized infection the response of certain tissue groups proceeds in an orderly sequence. This is subject only to modifying influences due to interference with the course of infection. Such interference may confer protection on tissue groups which ordinarily are early involved, and may bring into reaction groups occupying positions further on in the sequence. These experiments are particularly interesting to us because syphilis of the eye, which is usually one of the latest tissue groups to be involved in rabbits, frequently occurs and recurs under conditions which confer the greatest protection on other tissue groups. This indicates not only a low susceptibility of this group to the infection, but both an inherent inability for defense, and a lack of protection by the general reaction. The authors suggest the possible bearing of this observation on the genesis of neurosyphilis.

By the "law of inverse proportions" is meant an inverse quantitative relationship that exists in the intensity of consecutive reactions to syphilitic infection. It has been shown that the local primary tissue reaction following inoculation plays a dominating rôle in the elaboration of defense. Suppression of this local reaction by whatever means modifies the animal's status so that clinical manifestations of generalized syphilis usually develop. Conversely, the greater the local primary reaction and the more extensive the resulting primary lesion, the less likely are generalized clinical manifestations to occur. In other words, focal lesions by intensive reaction confer protection on tissue remotely situated about other foci of infection. Subcurative doses of treponemocidal drugs by suppressing

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the initial lesion produce this inverse condition in rabbits: an observation analogous to what is observed when human syphilis is inadequately treated during the primary and early secondary periods. The significance of this analogy is the more obvious when it is remembered that the period of chancre in the rabbit ordinarily is the only early reaction, and therefore corresponds to the entire period in the human being during which primary and early secondary reactions appear.

INFLUENCE ON SYPHILIS OF CENTRAL NERVOUS SYSTEM

As these phenomena are identical with those observed in human syphilis, they may be accepted as fundamental. The central nervous system occupies a position toward the end of a tissue group sequence, because it is not only less susceptible, but also less reactive. It is in this sense that neurosyphilis differs fundamentally from other tissue reactions in syphilis. The incidence and gravity of neurologic reaction is regulated by antecedent tissue reactions in other parts of the body, either by a degree of protection conferred, or by the lack of such protection. The influence of immunity on the genesis of neurosyphilis is greater or less, therefore, because of the operation of the "law of inverse proportions." The secondary phenomenon of hypersensitiveness, however, operates here as it does elsewhere in tissue groups, with the difference due to the remote position in the sequence which nervous tissue occupies, so that hypersensitiveness has greater force because of its fuller development. If there is a normal condition of susceptibility and reactivity of nervous tissue, therefore, neurosyphilis will depend on the balance between the infection, on the one hand, and the protective and hypersensitive immune reactions, on the other.

Investigations of numerous observers make it probable that the central nervous system is invaded in all patients contracting syphilis. Clinically, however, we know that less than 50 per cent. of these patients are

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neurosyphilitic. In the syphilis department of the Johns Hopkins Hospital, 21 per cent. of all late syphilitics, including cases of latent syphilis, present definite clinical neurosyphilis on admission. In addition to this, 21.6 per cent. of late syphilitics with apparently normal nervous systems have definite abnormalities in the cerebrospinal fluid permitting the diagnosis of late asymptomatic neurosyphilis, making a total of 42.6 per cent. of all patients with late acquired syphilis who are actively neurosyphilitic. This figure represents the percentage of all late syphilitics in our clinic who have failed to acquire an immunity sufficient to suppress the neurologic invasion.

PROTECTION OF NEURAXIS BY IMMUNE REACTIONS

Evidence of immune protection is suggested in an additional 17.7 per cent. of all late syphilitics. These are patients presenting minor neurologic abnormalities not in themselves diagnostic of neurosyphilis, but suggestive indications of early neurologic damage, in whom the spinal fluid is nevertheless normal. In view of what we already know, it is probable that these are instances of neurolatency, the so-called "burnt out" neurosyphilis in which spinal fluid abnormalities have disappeared. The remaining 39.7 per cent. are patients with apparently normal cerebrospinal fluids, in whom neurolatency has developed without demonstrable neurologic damage, or who have developed protection before damage has been done.

Viewed from another angle, we have been able to show by statistical studies [3] that in early asymptomatic neurosyphilis the character of antecedent tissue reactions markedly modifies the incidence of cerebrospinal fluid abnormalities. Thus, patients who have had mild or average generalized outbreaks show evidence of neurologic damage with greater frequency than do

3. Moore, J. E.: Studies in Asymptomatic Neurosyphilis, II, The Classification, Prognosis and Treatment of Early Asymptomatic Neurosyphilis, Bull. Johns Hopkins Hosp. 33: 231 (July) 1922.

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those who had severe secondary lesions. In late syphilis, also, it is significant that the incidence of late asymptomatic neurosyphilis is only 18.4 per cent. in the patients presenting tertiary lesions outside the central nervous system, compared with 24.6 per cent. in patients free from such lesions.

INFLUENCE OF ADEQUATE AND OF INADEQUATE TREATMENT

The figures arrived at in these studies, however, do not represent the influence of natural immunity only, but must be revised by determining the influence of at least two other factors, namely, early treatment and pregnancy. The influence of treatment on the development of immunity depends on the degree of the patient's preliminary reaction to the infection, on the time at which treatment is begun, and on the intensity, continuity and duration of the therapeutic attack. The immediate effect of treatment in primary and early secondary syphilis is depressant on the mechanism of immunity, possibly to the extent of producing a negative phase in sensitized patients, because it serves to destroy the excitant to immunity production before the process has reached protective proportions. A short course of intensive treatment in these cases, insufficient to destroy the infection completely, produces a condition of low infectivity with little or no protection, analogous to that produced in the experimental animal by a subcurative dose of arsphenamin. As a result, it might be predicted that such patients may later develop grave lesions, especially in tissues ordinarily late to be involved. That this does happen is demonstrated by a study of the incidence of neurorecurrences in such a group in this clinic. Of approximately 800 inadequately treated patients with early syphilis, about 5 per cent. developed neurorecurrences within the first months of the disease.[4] Furthermore, a study of a

4. Zimmermann, E. L.: Neurorecurrences after Arsphenamin, Arch. Dermat. & Syph. 5: 723 (June) 1922.

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large number of cases of early syphilis insufficiently treated shows an incidence of early asymptomatic neurosyphilis three times greater than that in adequately treated patients.[3]

On the other hand, prolonged courses of adequately intensive, continuous early treatment have the effect of greatly reducing the incidence of neurosyphilis. As this more especially represents a causal effect other than that due to immune reactions, it need not be illustrated here. It has been suggested, however, that this type of treatment protects the patients not only by virtue of its parasiticidal action, but possibly also by increasing eventually the activity of the natural protective processes.[5] Concerning the latter action, there is as yet insufficient evidence of a positive character so that it is hardly justifiable to attempt to evaluate its influence at this time. If the initial reaction to the infection has been vigorous and extensive before treatment is begun, and the time relation necessary for the elaboration of immunity has not been disturbed, a short course of treatment seldom, if ever, leads to neurorecurrences, and the incidence of abnormalities in the cerebrospinal fluid is not increased.

POSSIBLE RELATION OF PREGNANCY TO IMMUNE PROCESSES

The relative infrequency of clinical neurosyphilis in women as compared with men is a matter of common observation. In spite of the fact that, in early syphilis, invasion of the neuraxis occurs with equal frequency in the two sexes, three times as many men as women develop clinical manifestations of neurologic damage. In searching for the explanation of this apparently anomalous condition, pregnancy as the chief point of difference in the life history of the two sexes has been investigated by Moore of this clinic.[6] Pregnancy

5. Toyama, I., and Kolmer, J. A.: The Influence of Arsphenamin and Mercuric Chloride upon Complement Antibody Production, J. Immunol. 3: 301 (July) 1918 (extensive bibliography).

6. Moore, J. E.: Studies in Asymptomatic Neurosyphilis, III, The Apparent Influence of Pregnancy on the Incidence of Neurosyphilis in Women, Arch. Int. Med., to be published.

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greatly modifies the reaction to syphilitic infection, the tendency being to suppress lesions and induce latency. The incidence of neurosyphilis in women who have been childless is equal to that in men, while its incidence in women who had been pregnant since their initial infection is only half that of the nonpregnant group.

This protection conferred through pregnancy may be a distinct mechanism apart from natural immunity, or it may be the result of altered conditions leading to a more pronounced development of the natural protective mechanism. It is, nevertheless, a factor of great importance in the natural protection of syphilitic women.

SUMMARY

Since neural invasion occurs in probably all cases of early syphilis, and the incidence of late symptomatic and asymptomatic neurosyphilis is limited, it is probable, if not certain, that immune reactions protect the neuraxis. The character of the early tissue reaction to syphilitic infection, the intensity, continuity and duration of the therapeutic attack, and the occurrence of pregnancy in women, markedly modify the incidence of neurosyphilis, both clinical and asymptomatic. An analogy exists between these factors in human syphilis and the laws of progression and inverse proportions in animal syphilis.

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FLUMERIN—A NEW MERCURIAL FOR THE INTRAVENOUS TREATMENT OF SYPHILIS

FIRST REPORT OF CHEMICAL, ANIMAL AND CLINICAL EXPERIMENTS AND RESULTS *

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BALTIMORE

Experience in recent years has made it increasingly evident that the present day treatment of syphilis is not entirely satisfactory, partly owing to the fact that our attack on the disease is not sufficiently varied. It is generally agreed that efforts to improve on arsphenamin and neo-arsphenamin have been so far unavailing. It is also admitted that these drugs, either with or without mercury, constitute our most powerful antisyphilitic remedies, especially in early syphilis. In most cases (and in all instances of late syphilis) mercury in some form must be employed. A few patients, moreover, fail to tolerate the arsphenamins, and complete reliance must then be placed on mercurial treatment.

The four common methods of administration of mercury, by ingestion, intravenous injection, intramuscular injection, or inunction, are open to various objections. All these methods are of value, but all fall short of the desired ideal. As far as intravenous injection is concerned, the compounds of mercury in common use

* This investigation has been aided by a grant from the United States Interdepartmental Social Hygiene Board.

* From the James Buchanan Brady Urological Institute and the Syphilis Department of the Medical Clinic, Johns Hopkins Hospital.

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(mercuric chlorid, cyanid, oxycyanid, benzoate, succinimid) are limited in value either by comparatively high toxicity or by their local corrosive action.

We have attempted, therefore, to develop a mercurial drug suitable for intravenous injection, in which would be combined the three factors of therapeutic value in animal and human syphilis, low toxicity and absence of local irritating qualities. The drug which forms the subject of this paper has these advantages. It is well to state that we do not believe that this drug, or any mercurial so far developed, can supplant the arsphenamins. We attempt to demonstrate only the three advantages mentioned and to suggest that further experience may show this drug to be of more value than other mercurials now in use by the intravenous route. We do not suggest that the intravenous route is the best method of administration of mercury, and we do not wish to be interpreted as advocating any special plan of treatment for syphilis.

CHEMISTRY OF FLUMERIN

The field of search lay obviously among the organic mercurials, substances in which the mercury atom is bound directly to a carbon atom. In solutions of such compounds, the mercury is in a nonionic condition. In an earlier research on penetrating disinfectants, which led to the development of mercurochrome,[1] a number of mercury derivatives of various phthaleins were prepared by one of us (E. C. W.). Laboratory tests on these compounds included, of course, determinations of their toxicity for animals; and from this standpoint the substance described in this paper stood out as having very low toxicity, although it was discarded as a local disinfectant because it did not show as marked penetration of tissue as did the other members of the series, and because it was comparatively low in bactericidal power.

1. Young, H. H.; White, E. C., and Swartz, E. O.: A New Germicide for Use in the Genito-Urinary Tract: "Mercurochrome-220", J. A. M. A. 73: 1483 (Nov. 15) 1919.

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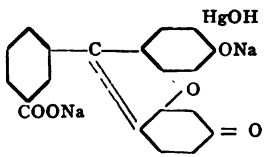
Although low toxicity is perhaps the best lead in selecting a mercurial drug from a series for study in the treatment of syphilis, it must be pointed out that this property does not of itself mean that the drug will have practical usefulness. Only if it can be shown that there is a concomitant marked therapeutic effect in animals are we justified in believing that the low toxicity will be an asset of clinical value. For this reason, the present study has included a description of chemistry of the drug, toxicity determinations, a study of the effect of the drug on rabbit syphilis, and finally a careful clinical study.

Description of the Drug.—The drug is the disodium salt of hydroxymercurifluorescein [2] (whence the simplified name flu-mer-in) whose chemical formula is:



It forms a dark red powder with greenish iridescence and is easily soluble in water, especially hot water, up to about a 10 per cent. solution. The solution used clinically (2 per cent.) is stable to the air and to heat; in fact, solution of the powder is best effected by using hot water, although it is easily, though less rapidly, soluble in cold water. The powder is stable indefinitely in air, except that it is somewhat hydroscopic and should, therefore, be kept in well stoppered bottles or in ampules. As the drug has disinfecting value about equal to that of phenol, the solution may be considered

2. To avoid misunderstandings, reference is made to two German patents, Nos. 201903 and 308335, dealing with mercury derivatives of phthaleins. At this time, it is only necessary to say that the process employed in the preparation of flumerin is fundamentally different from those of the patents mentioned, and leads to an essentially different product. Discussion of the technicalities involved would be out of place here, but will be entered into in detail in a later chemical paper. It is interesting to note that Klages and Schreiber (Seventeenth International Congress of Medicine, 1913, Transaction of Section of Therapeutics, pp. 65-71) made a clinical trial of some of the patented substances, including the derivatives of fluorescein. The therapeutic effects were so slight that further clinical use was not considered.

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self-sterilizing. Although we have used, clinically, solutions as old as 3 or 4 days, it is best to use only freshly prepared solutions made up in sterile, freshly distilled water. Exposure to the air for several hours does not alter the solution chemically. On long standing (one week or more), a slight precipitate of metallic mercury as a gray powder is sometimes seen.

Solutions of the drug give no precipitate with caustic alkali, iodids or ammonium sulphid, with the exception that the latter forms mercuric sulphid on long standing in the cold or in a short while on boiling. There is complete absence of precipitation when the solution is mixed with serum. This nonprecipitating action on protein accounts for the blandness of the drug toward tissues.

The drug contains about 32.5 per cent. of metallic mercury, as against the theoretical content of 33.8 per cent. required by the formula $C_{20}H_{10}O_6Na_2Hg$. The difference is due to moisture and a small amount of unmercurated fluorescein salt, which is quite inert. The 2 per cent. solution is hypotonic, showing a freezing point lowering of 0.14 C. as against an average value of 0.56 C. for normal blood serum.

TOXICITY OF FLUMERIN FOR ANIMALS

Toxicity has been determined on rabbits and dogs, always using intravenous injection. Rabbits uniformly tolerate a single dose of 30 mg. per kilogram. This is often followed by the appearance of albumin or casts, or by a decrease in phenolsulphonephthalein output, or by all three. The damage is transient, and usually within a week the phenolsulphonephthalein excretion, if lowered, returns to normal, and the urinary abnormalities disappear. This dose is usually followed by definite loss in weight. Of four rabbits receiving 40 mg. per kilogram, two died within twenty-four hours, and two survived. Fifty mg. per kilogram was fatal in all cases. Repeated small doses of 5 or 10 mg. per

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kilogram have been given in a series of as many as twenty doses, at intervals averaging two or three days. This rarely led to any urinary abnormality or phenolsulphonephthalein decrease, although some animals lost weight under continued medication. In this respect, there is great variation among individuals. Likewise, diarrhea has been observed occasionally, but its incidence has been so variable that it cannot be linked with size or number of doses.

The toxic limit is about the same in dogs, which usually die within twenty-four hours after a single dose of 50 mg. per kilogram, although a few have survived this amount. This dose always causes violent retching and diarrhea shortly after the injection, and the animal appears very sick. Blood in the rectum and mouth has been observed in some animals dying from such an injection. Thirty mg. per kilogram is well tolerated, although there is sometimes transient evidence of kidney damage. Loss in weight is less frequent and less marked than in rabbits receiving the same dose. Repeated doses, at average intervals of two or three days, of 10 mg. per kilogram are well borne, and as many as twenty doses of 5 mg. per kilogram are well tolerated by strong, healthy dogs, with no loss in weight and no evidence of kidney injury.

On the basis of the figures given by Schamberg, Kolmer and Raiziss [3] as to the toxicity of various common mercurials suitable for intravenous injection, it is apparent that, by this route flumerin is tolerated by animals in amounts more than six times as great as any of the usual preparations; as utilized clinically, the average dose is twenty times that of the cyanid, benzoate, mercuric chlorid or succinimid, and in equivalent mercurial content is about eight times as large.

Pathologic studies on animals experimentally killed by large single doses, and sacrificed after repeated small

3. Schamberg, J. F.; Kolmer, J. A., and Raiziss, G. W.: A Study of the Comparative Toxicity of the Various Preparations of Mercury, J. Cutan. Dis., December, 1915.

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doses, have been carried out by Drs. W. A. MacCallum and J. R. Cash. These studies, as yet incomplete, will be reported in detail in connection with a series of experimental and clinical papers to appear later.

THE VALUE OF FLUMERIN IN EXPERIMENTAL SYPHILIS

The chemotherapeutic investigations of Brown and Pearce on arsenicals, and of Schamberg, Kolmer and Raiziss on mercurials, have conclusively demonstrated that the therapeutic ratio of a given drug in protozoan infections other than syphilis, for example, trypanosomiasis, relapsing fever or chicken spirillosis, cannot be considered accurate for syphilis. Mercurials have in general little or no effect on trypanosome infections. We have, therefore, confined the testing of the therapeutic action of flumerin to syphilis in the rabbit.

This method of therapeutic experimentation has fortunately become much more accurate than formerly, because inoculations of animals with infectious material are always successful, the incubation period is well defined and a complicating cause of resolution of lesions may be eliminated by avoiding their aspiration. Most important, the former indefinite end-point of therapeutic activity, namely, the resolution of lesions and prolonged observation of the animal for relapse, has been replaced by the method of transfer of lymph nodes from treated animals to normal rabbits. This offers not only a definite end-point, but also provides more rigid criteria of cure.

Method.—Through the kindness of Dr. Wade Brown, a rabbit was secured with a testicular infection of the Nichols strain of *Spirochaeta pallida.*[4] From this rabbit, the strain has been continued by two methods. By the first,[5] an infected testicle was excised

4. Nichols, H. J., and Hough, W. H.: Demonstration of Spirochaeta Pallida in the Cerebrospinal Fluid, J. A. M. A. **60**: 108 (Jan. 11) 1913.
5. Brown, W. H., and Pearce, Louise: Experimental Syphilis in the Rabbit, I, Primary Infection in the Testicle, J. Exper. Med. **31**: 475 (April) 1920.

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under ether anesthesia, emulsified in a small amount of sterile 0.85 per cent. salt solution, the presence of spirochetes determined by dark-field examination, and normal rabbits injected intratesticularly, in most instances unilaterally, with not more than 0.5 c.c. each of this emulsion. By the second method,[6] under ether anesthesia, the popliteal or inguinal nodes were excised, emulsified in a small amount of sterile salt solution, and, regardless of dark-field findings, normal rabbits were injected intratesticularly with not more than 0.5 c.c. each of the emulsion.

Treatment with flumerin was carried out in animals with fully developed lesions. A study of the action of the drug on very early lesions, at present in progress, indicates that it is more difficult to influence the infection at the time of first appearance of lesions than later. Treated animals, in which resolution of lesions occurred, were held under observation to allow the infection to become reestablished. If no relapse took place, transfers of the popliteal nodes were then made to the testicles of normal rabbits, which were observed for an average of seventy-nine days. If the transfer animals failed to develop lesions and if organisms could not be found in popliteal or inguinal nodes at the end of the period of observation, we felt justified in concluding that the action of the drug had been sufficient to destroy the organisms in the regional lymphatics, where Pearce and Brown[7] have shown that spirochetes may be found on and after the second day after inoculation in untreated animals. Careful controls were made on every series of experiments.

Experiments.—Our experiments have fallen into two groups: animals treated with repeated small doses, and those treated with single large doses. In every case,

6. Brown, W. H., and Pearce, Louise: Latent Infections with the Demonstration of Spirochaeta Pallida in Lymphoid Tissues of the Rabbit, Am. J. Syph. 5: 1 (Jan.) 1921.

7. Pearce, Louise, and Brown, W. H.: A Study of the Relation of Treponema Pallidum to Lymphoid Tissues in Experimental Syphilis, J. Exper. M. 35: 39 (Jan.) 1922.

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the drug was given intravenously. The tolerated single dose of flumerin for rabbits by this method is, as has been stated, 30 mg. per kilogram.

Series I: Using Repeated Doses of 10 Mg. per Kilogram.—Five animals were given from four to eight doses of 10 mg. per kilogram, the drug being given every other day. In four, there was prompt resolution of lesions; the fifth, in which the local lesions had resolved, but which was known to be syphilitic, was treated during the latent period. These animals were held an average of thirty-five days after the last dose. At the beginning of these experiments, the value of lymph node transfer had not been demonstrated, but transfers of the popliteal nodes of two of this series failed to produce lesions in the transfer animals during eighty days of observation.

Series II: Using Repeated Doses of 5 Mg. per Kilogram.—Five animals were given an average of ten daily doses of 5 mg. per kilogram. Resolution began promptly and was complete in an average of eight days. At an interval of thirteen days after the last dose in four animals, and twenty-five days in the other, popliteal node transfers were made. One of the transfer animals failed to develop lesions during fifty-seven days' observation, the others remaining negative during seventy-seven days.

Series III: Using Repeated Doses of 3 Mg. per Kilogram.—Five rabbits were given twelve daily doses of 3 mg. per kilogram. The results of this treatment varied strikingly. In one animal, lesions resolved, and node transfer made forty-nine days after the last dose was negative during fifty-three days of observation. In a second, there was resolution of lesions, but node transfer made the fifteenth day after the last dose was positive in thirty-five days. In the third rabbit, the lesions persisted, and though spirochetes could not be found on the thirtieth day after the last dose, a node transfer was then made which proved positive in thirty-four days. In the other animals, lesions were not resolved, spirochetes being found in one the sixty-fifth day after the last dose. The remaining animal died by accident during the night, and although spirochetes could not be found at necropsy in the morning, the large lesions indicated the slight effect of the drug.

Series IV: Using a Single Dose of 30 Mg. per Kilogram.—Four rabbits were given this dose. In all, there was prompt resolution of lesions. Popliteal node transfers made twenty days after treatment were negative in three animals during ninety days of observation, and positive in one in forty-eight days.

Series V: Using a Single Dose of 20 Mg. per Kilogram.—Four rabbits were used in this series. In all, there was

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resolution of lesions. Node transfers from two animals made thirty days after treatment showed negative results during 101 days of observation in one, and positive results in the other in forty-three days. A third animal relapsed forty-five days after treatment, and spirochetes were found by dark-field examination. The fourth is still under observation.

Summary.—From four to eight doses of 10 mg. per kilogram, given on alternate days to a series of five rabbits with well established infection, caused resolution of lesions in every case, and in two instances in which node transfer was made no infection resulted in the transfer animals. An average of ten daily doses of 5 mg. per kilogram to a series of five rabbits caused resolution of lesions in every case, and popliteal node transfers were consistently negative. Twelve daily doses of 3 mg. per kilogram to a series of five rabbits gave conflicting results. In two animals, lesions resolved, and node transfer was negative in one, but positive in the other. In the remaining three, lesions persisted. A single dose of 30 mg. per kilogram caused resolution of lesions in four rabbits, negative node transfers in three cases and a positive node transfer in the remaining animal. One dose of 20 mg. per kilogram caused resolution of lesions in four animals, and later observation resulted in negative node transfer once, positive node transfer once, and relapse once; and one rabbit is still under observation.

In a single dose, therefore, the curative dose of flumerin, 30 mg. per kilogram, closely approaches the maximum tolerated dose; but a series of doses of 5 mg. per kilogram is uniformly effective. This is in sharp contrast to serial doses of 3 mg. per kilogram, which are usually ineffective.

CLINICAL APPLICATION OF FLUMERIN

The foregoing is a satisfactory demonstration that this drug is one of very low toxicity, and that in rabbit syphilis it has a definite curative effect. In single dose, its therapeutic ratio is, in common with that of other

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mercurials, 1 : 1; but repeated small doses are effective in eradicating rabbit infections, the standard of cure being based on rigid criteria. These data were considered sufficient to justify its use in human syphilis. Accordingly, a number of patients have been treated in the syphilis department of the medical clinic, under the direction of one of us (J. E. M.).

We have used flumerin alone in order that the results may not be obscured by the administration of arsphenamin.[8] Treatment has generally been continued at two-day intervals, until a course of from twelve to sixteen doses has been given. In most instances, patients presenting open lesions have been chosen so that the effect of the drug on the healing of lesions could be followed.

In spite of the low toxicity of flumerin in animals, it was considered advisable to begin in the human subject with doses smaller than the demonstrated curative dose in rabbits, in order to avoid possible untoward effects. For this reason, the first dose was usually 2 mg. per kilogram, and subsequent doses 3 mg. per kilogram. For a man, this is about 0.2 gm. Recently, we have administered as much as 5 mg. per kilogram, or about 0.35 gm., to a small number of robust patients, without demonstrable ill effects. These patients are still under treatment, however, and are not included in the present discussion of therapeutic effect or reactions. The results of this larger dosage will be reported in a separate clinical paper.

Ninety-six patients have been treated. Of these, five patients with primary syphilis, twenty-one with secondary syphilis, and twenty-four with various lesions of tertiary syphilis, received five or more injections of the drug, sufficient to permit the formation of an opinion as to therapeutic and possible toxic results. In addition are included ten patients who were intoler-

8. Since the toxicity of at least one of the halogen mercury compounds of fluorescein is much greater than that of flumerin, it is considered inadvisable at present to administer iodids concurrently because of the theoretical possibility of the formation of a toxic halogen mercurial compound in the body. A separate set of toxicity experiments, using an iodid and flumerin together, should be made.

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ant to arsphenamin, five who reacted badly to other methods of administration of mercury, four Wassermann-fast patients, and a few patients with latent or neurosyphilis. The remainder received only a few injections, and were then lost from observation.

The results on the whole have been good. In Table 1 are shown, in summary form, the data regarding the groups with open lesions.

Of the primary cases, three gave seronegative reactions on admission, the duration of the disease being three days, ten days, and seven weeks, respectively.

TABLE 1.—SUMMARY OF TREATMENT OF FIFTY CASES WITH FLUMERIN

Stage of Syphilis	Number of Cases	Lesions Healed	Average Number of Days to Heal Lesions	Serologic Result (Blood)		Average Number of Doses to Reduce Wassermann
				Good	Poor	
Primary.....	5	4	22	4	1	3 remained 0 1 case, 12 doses
Secondary...	21	21 (relapse in 1 case)	19	11	10	8
Tertiary.....	24	19 (improved in 5 cases)	25	9	15	10

(The last patient had received two doses of arsphenamin, beginning at the fifteenth day of his disease. He developed a typical arsphenamin dermatitis after the second dose, and was transferred to flumerin for this reason. At the time of transfer, his lesions were still unhealed.) In all three of these cases, the blood Wassermann reaction remained permanently negative during and after treatment with flumerin. One patient had a seropositive reaction on admission which became permanently seronegative after the twelfth dose of flumerin fifty-three days after starting treatment, though a break in the Wassermann reaction was obtained eight days earlier. The length of time necessary to bring about this result is probably due to a long lapse in treatment, twenty-three days intervening between the first and second doses.

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With one exception, the primary lesions were healed in an average of twenty-two days, the shortest time being fourteen days (after five doses of the drug), the longest thirty days (after four doses). The one case in which healing failed to occur was that of a man with a typical diphtheritic chancre of three days' duration, in which spirochetes were demonstrated. His blood Wassermann reaction was negative. After seven doses of 3 mg. per kilogram, the initial lesion was still unhealed and had definitely spread. At this time, sixteen days after starting treatment, no spirochetes could be found. A week later, two more doses of flumerin having been given without healing, this drug was discontinued, and a course of eight doses of arsphenamin substituted. The lesion healed very slowly, complete cicatrization occurring only after the sixth arsphenamin injection. At the completion of this series, he was put on mercury by inunction; but after three weeks of faithful application to this treatment, he returned with an ulceration in the indurated scar of the healed chancre. Many spirochetes were now demonstrated by dark-field examination. This case, therefore, is obviously resistant to arsphenamin, as well as to mercury, and can hardly be charged against flumerin as a failure.

In secondary syphilis, evidence of the therapeutic activity of the drug was also obtained. Of twenty-one cases, the blood Wassermann reaction was reduced to negative (in most instances permanently so) in eleven. This result was accomplished in an average number of eight doses (about three weeks of treatment). In another case, a break to suggestive negative was obtained after seventeen doses of flumerin. An additional patient, who had received numerous doses of antimony and potassium tartrate intravenously elsewhere because of the erroneous diagnosis of granuloma inguinale, had a negative reaction on admission, which remained so in spite of unmistakable lesions of early

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secondary syphilis. In the remaining eight patients, the blood Wassermann reaction remained positive throughout the course of treatment. Four of these, however, received only six injections or less.

All lesions were healed, the average time necessary (regardless of the type of lesions) being twenty-one days (seven doses of flumerin). In one patient, a man with enormous condylomas, the behavior of spirochetes was studied. Five hours after the injection of 3 mg. per kilogram, no spirochetes could be found, though on admission they averaged one to the high power field. Twenty-two hours after the injection three spirochetes only could be found after exhaustive search, while, after twenty-five hours, none were present.

One case was of particular interest. This was that of a colored girl with annulopapular lesions on the face, and moist papules about the genitalia. She was given sixteen doses of flumerin, the average dose being 3 mg. per kilogram, at fairly regular intervals, though treatment was twice interrupted because of stomatitis, for a week and ten days, respectively. Her original lesions were completely healed in thirty-one days, after eight doses of the drug, and at the same time a beginning reversal of her blood Wassermann reaction had occurred. The remainder of her treatment was uneventful until the day of the sixteenth injection, when she drew attention to a lesion on her lower lip, of two days' duration. This was a typical papulo-erosive mucous patch about 2 cm. in diameter, containing an enormous number of actively motile spirochetes. Her blood Wassermann reaction was still negative. This represents a clinical recurrence while under treatment, such as are practically never observed under arsphenamin therapy, though similar instances after administration of various types of mercurials are not uncommon.

To sum up with regard to primary and secondary syphilis: evidence is provided that in the dosage employed, 3 mg. per kilogram, flumerin is therapeutically active in the sense that it will cause spirochetes to

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disappear from lesions, will bring about the resolution of lesions, and, in about half the cases treated, will change a positive blood Wassermann to negative.

Twenty-four cases of tertiary syphilis, mostly gummatous or nodular skin lesions, have been treated. Several cases of bone syphilis are included in this total. All lesions were healed in nineteen cases, and in the remaining five were greatly improved. The average time of healing was twenty-five days. Nodular syphilids healed more promptly, the average being fifteen days; while skin gummas, ranging in diameter from 1 to 10 or 15 cm., took an average of thirty days to heal. A break in the blood Wassermann reaction, not always to a complete negative, was obtained in nine of the twenty-five cases, while in sixteen the test remained positive.

The groups of patients who tolerated arsphenamin or other forms of mercury badly are of interest, and the cases may be briefly summed up. Ten patients who had had an arsphenamin dermatitis have been treated with flumerin and have in every instance tolerated the drug well. The results are obscured by the previous treatment, but in two cases it has been possible to reduce a positive Wassermann reaction to negative. It is suggested that in patients of this type flumerin may prove a valuable addition to our insufficient armamentarium.

Five patients who tolerated badly mercury in other forms have been treated. Three of these, all patients with late syphilis, had repeatedly shown their inability to tolerate mercury by inunction. In each instance, after a week or two of rubs, salivation, headache or severe bone pains always occurred. Each of these persons tolerated from eight to twelve doses of flumerin, 3 mg. per kilogram, without reaction of any kind. The remaining two suffered from recurring eye lesions each time mercury by inunction was attempted, though arsphenamin promptly controlled the lesions. In the first, a case of recurrent iritis and neuroretinitis, flumerin

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was begun after the third course of arsphenamin, in the attempt to avoid the recurrences of the first and second course of inunctions. The result was satisfactory—no recurrence developed. The second patient was put on flumerin during his fifth recurrence of iritis, which healed promptly—a result never obtained in that patient by inunctions.

Reactions.—There were no local reactions observed from the use of this drug. It is nonirritating to veins, and thrombosis has never occurred, even after many injections. In a few instances in which the drug has been injected outside the vein, a moderately painful swelling, lasting about twenty-four hours, has resulted. No sloughs have been observed.

TABLE 2.—GASTRO-INTESTINAL REACTIONS FROM FLUMERIN

Total Number of Doses Given	Number of Injections Followed by				
	Immediate Nausea or Vomiting			Diarrhea	
	Mild	Severe	Cramps	Mild	Bloody
945	22 (2.3%)	19 (2.01%)	7 (0.7%)	10 (1.0%)	8 (0.9%)
	41 (4.3%)				

The general reactions observed may be separated into three groups: (1) gastro-intestinal; (2) stomatitis, and (3) renal irritation. In Table 2, it is shown that, of 945 doses of the drug, 66 injections (6.9 per cent.) have been followed by a reaction of the first group. For the most part they have been negligible, but occasionally a very severe reaction is observed. Fairly commonly, a patient complains of nausea, either actually during the injection of the drug or within five minutes afterward. This is usually mild in character and lasts only a few moments. Less frequently it is quite marked and is associated with very severe retching and vomiting. Even in these cases, however, the discomfort disappears spontaneously within half an hour, and usually there is no after-result. In a few patients, such reactions have tended to recur after succeeding

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injections, and twice it has been necessary to discontinue the drug for this reason. The rapidity with which the reaction appears suggests that it may be central in origin. Four per cent. of all injections have been followed by reactions of this type, equally divided between mild and severe. Dosage, the number of injections given, the concentration of the solution, or the speed of administration, seems to play no rôle in the development of these reactions.

Seven injections were followed in a few hours by abdominal discomfort or cramps, and eighteen (1.9 per cent.) by diarrhea, which in eight instances, according

TABLE 3.—REACTIONS FROM FLUMERIN

Total Number of Patients	Stomatitis		
	Total Cases	Mild	Severe
96	36 (37.5%)	30	6 (6.2%)
	Urine Examinations		
	No Change	Existing Abnormalities Cleared up Under 205	Transient Albuminuria or Casts During Treatment
77	50	10 (12.9%)	17 (22%)
	Phenolsulphonephthalein Output		
	No Change	Increased Plus 15 or More	Decreased Minus 15 or More
61	49	9 (14.7%)	3 (4.9%)

to the patient's report, contained blood. Two patients had to be transferred to arsphenamin because of bloody diarrhea.

Of the total number of ninety-six patients treated, more than one third complained, at some time during the course of treatment, of sore mouth, gums or teeth. In the majority of cases, this was subjective only. Nothing could be seen on examination, and the continued administration of more drug did not make the condition worse. On the contrary, it usually cleared up spontaneously, even when further injections were given. In six cases, an actual stomatitis, with swollen, bleeding gums, ulceration behind the last lower molar, etc.,

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occurred. In all instances, this was comparatively mild, and cleared up as soon as the drug was stopped.

Aside from this, and the gastro-intestinal reactions already detailed, the use of flumerin has been attended by practically no subjective complaint. These reactions are less frequent than after the arsphenamins or an equivalent amount of other mercurials.

Particular attention has been paid to the possibility of renal damage. Urine examinations have usually been made at every visit, phenolsulphonephthalein tests have been made before and after treatment, and, in a few cases, the blood chemistry has been studied. Of seventy-seven patients in whom adequate urine examinations had been made, the urine showed no change in fifty. In ten instances (12 per cent.), albuminuria or cylindruria present on admission was cleared up by the end of treatment with flumerin. In seventeen cases (22 per cent.), a transient albuminuria or cylindruria developed during treatment, but cleared up promptly on cessation of the drug. In four instances, both albumin and casts appeared, in nine cases albumin only, and in four casts only. These figures are based on a dosage of 3 mg. per kilogram. Recent experience, using 4 or 5 mg. per kilogram, shows no higher incidence of urinary abnormalities, though the data regarding these dosages are not included in this paper. Judging from the urine examinations, therefore, no permanent renal damage was done by flumerin.

Confirmation of this is afforded by the phenolsulphonephthalein results. In thirty-six of sixty-one patients, the last test was the same as the first. In nine instances (14.7 per cent.), the phenolsulphonephthalein output was fifteen or more points higher at the end than at the beginning of treatment, while in three cases (4.9 per cent.) only was there a drop of fifteen or more points (—25 once [artefact?], —15 twice). Blood chemistry studies before and after treatment have also been negative. Not only is evidence

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of nephritis lacking, but it is also apparent that the functional renal abnormalities caused by syphilis have frequently disappeared after the administration of flumerin.

This drug is, therefore, singularly free from serious reactions in the dosage which we have employed.

COMMENT

The evaluation of the worth of any new drug in medicine, and particularly in the treatment of syphilis, is a difficult problem, which must be approached with the utmost caution. In this instance, it is fraught with special difficulties. It is obvious that flumerin cannot be compared with the arsphenamins. No strictly comparable studies with other mercurials, especially so far as rabbit syphilis is concerned, have been carried out. It is not permissible to conclude, because the single dose therapeutic ratio of this drug is the same as that of other mercurials, and because a quantity of flumerin from eight to twenty times greater than other mercurials can be safely employed, that the actual therapeutic activity of flumerin is, therefore, proportionally greater. Therapeutic activity depends on many other factors, chief among which may be mentioned the penetrability of a given drug, and its ultimate fate in the body. No comparisons are therefore attempted, and it is given only as our clinical impression that flumerin is, from the standpoints of toxicity and therapeutic activity, superior to the soluble mercurial salts in general use by the intravenous route.

No attempts have as yet been made to employ the drug by the intramuscular route. For the present, and until adequate experimentation shall have demonstrated the limitations of toxicity, the factor of freedom from pain and the relative value of this route as compared to the intravenous route, we do not advise its use.

From the standpoint of the clinical results, it should be pointed out that, as yet, we have given only small

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doses of the drug. The results obtained in rabbit syphilis indicate the desirability of employing doses larger than 3 mg. per kilogram. The few instances in which we have recently administered 4 or 5 mg. per kilogram indicate that the effect of the drug on lesions and on the Wassermann reaction is enhanced. Attempts to increase the dosage must, however, be carried out cautiously and under adequate control.

No attempt is made to suggest the ultimate place which this drug may attain in the treatment of syphilis. It is not available for general distribution, and, for the present at least, permission will not be granted for its commercial manufacture.

SUMMARY

This paper deals with a new soluble mercurial drug of low toxicity and of remarkably nonirritating character when injected intravenously. The complete chemical name—hydroxymercurifluorescein—has been shortened to flumerin. This drug is effective in eradicating experimental syphilis in rabbits in doses which are well tolerated. Even in large doses, it causes little or no clinical injury to the kidneys of animals. In ninety-six human cases, definite proof of its value as an antisyphilitic drug has been given.

Doses containing from eight to twenty times the amount of mercury present in the therapeutic dose of other mercurial drugs commonly used intravenously have been given with impunity, and the maximum dose which may be employed serially in the human being has not yet been determined.

The therapeutic effect of the drug has been shown in primary, secondary and tertiary syphilis by the resolution of lesions and the reversal of positive blood Wassermann reactions. The number of cases treated is sufficient to demonstrate that this mercurial is of value, but is too small to permit the allocation of the drug to a definite place in the therapy of syphilis.

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ABSTRACT OF DISCUSSION

ON PAPERS OF DRS. KEIM AND WILE, KEIDEL, AND WHITE, HILL, MOORE AND YOUNG

Dr. Udo J. Wile, Ann Arbor, Mich.: I can add very little to what Dr. Keim has said about this test, except to emphasize that it embodies certain features that are simplifications of our standard Wassermann reaction. It commends itself by the fact that all those tests which would ordinarily be 4 plus with the standard Wassermann reaction can be read within one hour after the blood has been drawn. Secondly, the use of a single substance in the performance of the test, together with a small quantity of blood serum, leads certainly to the hope that we are on the way toward a possible standardization of this test. Surely, if a test is so simple that it requires only a single substance plus the suspected blood serum and the complete elimination of the many details and sources of error which are found in the employment and nomenclature of the hemolytic system, that test is deserving of careful scrutiny for general application. It must be remembered that we have used this test in only a small number of cases. Three hundred cases tested clinically is really a very small number on which to base conclusions. This test has been used about 8,000 times, not clinically but in the department of health in Lansing, where its author, Dr. Kahn, compared it from the serologic standpoint with the Wassermann reaction, and I believe that it is on the way to a permanent place in the serology of syphilis.

Dr. R. L. Kahn, Lansing, Mich.: The limited time at Dr. Keim's disposal necessarily did not give him an opportunity to discuss the principle of the reaction. I will therefore take the liberty to say a word about it. Briefly, the antigen is so prepared that it contains a concentrated amount of antigenic substance and is diluted with physiologic sodium chlorid solution for the tests, with a view to rendering the final mixture as unstable as possible. This instability is brought about by adding as little salt solution to the alcoholic antigen as possible, rendering the diluted mixture on the verge of precipitation. This mixture is opalescent and clear, and will remain so at warm room temperature; but placed in the icebox, it will precipitate. The antigen is thus quite sensitive to precipitation. Therefore, when properly mixed with syphilitic serum, the antigen molecules readily react with the combining molecules of the serum, and marked precipitation results. Dr. Wile said that in the state health department at Lansing, about 8,000 tests had been made. This, I think, is based on a statement made months ago. We have now a record of more than 12,500 precipitation tests in the state laboratory. Most of these tests, however, lack definite clinical histories. The combined laboratory and clinical study of Dr. Keim and Dr. Wile, therefore, is of the

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utmost importance. For my part, it can only serve as a stimulus to try to perfect the test as much as possible, with a view to rendering it an important aid in the diagnosis of syphilis. With regard to spinal fluids, we are still in the experimental stage. We hope, in the course of months, to have this test apply to spinal fluids as well. The paper presented by Dr. Keim and Dr. Wile is based on the third communication of this precipitation test, which is to be published.

Dr. James Herbert Mitchell, Chicago: I should like to emphasize the importance of gland puncture in the early diagnosis of syphilis. Until about a year ago I thought very little of this, not having carried it out in any series of cases. Recently, however, I have carried this out as a routine procedure in all early cases of syphilis. Many times the chancre has been treated locally with various antiseptics, and often we do not see the chancre in public practice until three or four weeks have elapsed. At that time, especially after the application of antiseptics, it is very difficult to find spirochetes in the serum from the surface. Formerly we used to puncture the chancre at the root, but now we are puncturing the lymph glands. At first I used a small needle, believing that I obtained a better serum in that way; but now I use a large needle and leave it in the gland for two or three, or sometimes five, minutes, moving it about quite a little. Then with a very tight fitting syringe we aspirate gently. In practically all cases in which the glands in the region are large it is possible to get the organism.

Dr. Richard L. Sutton, Kansas City, Mo.: Dr. Driver referred to the importance of repeated Wassermann tests in cases that are negative to examination by dark field illumination. At times, it is extremely difficult to diagnose a suspicious primary lesion, and in many instances, only time and a number of serum tests will solve the problem. Should material from the lesion itself fail to contain spirochetes, serum, obtained by puncturing a contiguous lymph node, may prove fruitful. I believe that much of the criticism of the Wassermann test is due to the fact that in about 50 per cent. of cases the test is improperly or carelessly made. If it is too sensitive, we not infrequently get a false positive in a patient who is innocent of syphilis; if lacking in sensitiveness, a weak positive will be reported as negative. In one of our Kansas City laboratories, Dr. W. W. Duke and his laboratory chief, Miss Elizabeth Lease, have formulated a standard Wassermann test, or rather series of tests, in which I have grown to have great confidence. I cannot too strongly emphasize Dr. Keidel's plea for early and repeated examinations of the spinal fluid in patients with tertiary syphilis and neurosyphilis. It is a serious mistake to release a patient as "cured" until a careful examination of the spinal fluid has been made. I was also interested in Dr. Keidel's

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statement regarding the absence of gross skin manifestations in many, if not the majority of cases of syphilis of the nervous system. Dr. Charles White has called attention to the great frequency with which persons suffering from tabes and paresis give a negative history of skin syphilis, and I must acknowledge that I belong to that rather old fashioned school, the pupils of which believe that there exist certain strains of spirochetes which possess an affinity for certain tissues, such as the skin and the spinal cord. Dr. Moore and his associates have done an interesting and, I believe, valuable piece of work, and the remedy which they have introduced should find a broad field in the treatment of those patients who are very susceptible to arsenic.

Dr. John E. Lane, New Haven, Conn.: I was particularly interested in the relatively high percentage of ulcerative and gangrenous balanoposthitis found in Dr. Driver's series of penile lesions. Attention has not been called to this disease sufficiently, although Donovan's paper on the subject a year or two ago attracted considerable attention. The extremely rapid destruction of tissue which takes place when this condition is not recognized early makes its early diagnosis of the utmost importance, whether it exists alone or in combination with a chancre. I have found that this condition does not respond as well to intravenous injections of arsphenamin as does the Vincent infection in the mouth. I should like to know whether others have had the same experience. I was much interested in Dr. Moore's paper, but was rather disappointed that he did not compare the toxicity, therapeutic results and accidents following the use of the new compound, with those of the best mercurial compound we have previously used intravenously, mercuric cyanid. It would seem that a comparison of this sort should be made and that a probable superiority of the new compound should appear from the comparison in order to make a convincing argument for the adoption of the new compound. I should like to hear Dr. Moore's impression of this, even though he may have no experimental data on the cyanid. From the minor accidents following the injection of the new mercurial as described by Dr. Moore, I should infer that they are more frequent and somewhat more troublesome than they are following the use of mercuric cyanid.

Dr. Harry G. Irvine, Minneapolis: The figures of Dr. Driver on the difficulty of making an early diagnosis in syphilis are not only very interesting but also of extreme importance. I was much interested in the failure with results after something had been used on the chancre in the way of antiseptics. I should like to call attention to the work of Kolmer on the Wassermann test of serum from the chancre. For the past year we have been doing some work along this line, and have confirmed his work with forty or fifty cases. These have been proved later, either by clinical

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symptoms or finding of spirochetes, and so far as we have gone we have been able to show the presence of a positive Wassermann reaction in the serum from the initial lesion. I think this is important, and it may be that before long physicians will be able to send in serum from the lesion as they now send the blood for a test, and we may then make the diagnosis much earlier.

Dr. William Allen Pusey, Chicago: One of the points Dr. Keidel made should not pass without more comment than it has had, and that is the importance of the early immunity produced when syphilis is allowed to run its course. It is interesting to find that this work is confirming the early view that the uncured early treated case of syphilis was in worse shape than the patient who had been allowed to go on and develop his immunity. The experiments of Moore and Pearce are along the same line as the experiments reported today, and we should not let pass the importance of the observation that was made.

Dr. Joseph Grindon, St. Louis: In reference to the intravenous use of mercury in syphilis, I wish to call attention to the fact that in the medical history exhibit at the library of the St. Louis Medical Society, among many other interesting things, there is a copy of the Acta Philosophica of the British Royal Society, published in 1674, giving an account of the treatment of syphilis by the intravenous injection of a mercurial solution, done in 1668. Also an English translation of the Latin original by Dr. L. C. Boisliniere of this city.

Dr. V. G. Vecki, San Francisco: I am really glad to see that the glands are being a little more appreciated as a pathognomonic symptom, for even in late syphilis the glands sometimes will tell us stories that the blood test cannot. Ravogli recently named the two different strains of spirochetes, the neurotrope and the dermatrope. I had the opportunity to see the Molzer experiments in Munich. One strain he called his own, and another he got from Italy. With Plaut's system to obtain the spinal fluid of the rabbit without any admixture of blood, it was proved in many experiments that the Italian strain caused an increased cell count in the spinal fluid before any other symptom of syphilis appeared, or even any symptom to show that the inoculation was successful. That would prove that there are neurotrope strains; but if the German strain and the Italian strain show such a difference, how shall we explain the difference here in America? There are many questions to answer and one really does not know where to begin or where to stop. Of course, I also had my troubles with the Wassermann reaction, and I only hope that the Vernes colorimetric test, which is being investigated at the Columbia Hospital and which I have closely studied, and which, though fought for many years by the French medical profession, is now being

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endorsed by the president of the Pasteur Institute, Professor Brock and many other syphilographers, is going to solve the problem and enable us to make a periodic quantitative diagnosis and always receive the proper answer: Is there any syphilis or not?

Dr. James R. Driver, Cleveland: I am glad to hear Dr. Mitchell speak of gland puncture in making dark-field preparations. This procedure, especially in cases having had previous local treatment, should increase greatly our percentage of positive results. Our results so far by this method have not been very flattering, but with Dr. Mitchell's suggestions in mind we will try to improve our technic. Dr. Lain spoke of Vincent infections in the mouth reacting better to treatment than those on the genitalia. This has been our experience, if the infection involves the deeper tissues. What I wish to emphasize about erosive gangrenous balanitis is the early diagnosis, before the deeper structures are involved. In one of our cases there was almost complete destruction of the penis in one week's time, and in another there was total destruction of the scrotum in less than a week. We put these cases on soaks of hot potassium permanganate, 1:5,000 solution, for thirty minutes every four hours, alternating with hydrogen peroxid as a wash. The process clears up in a few days, but in the cases with extensive destruction a much longer time is necessary. Dr. Irvine's suggestion of early Wassermann tests on the serum from genital lesions is quite timely. This, in addition to our dark-field examination from the lesions, and from serum obtained by puncture of the regional lymph glands, I think, should make it possible to diagnose almost 100 per cent. of our primary lesions before the Wassermann reaction on the blood becomes positive. This would mean the possibility of curing practically all of our primary syphilitics if adequate therapy is given.

Dr. H. L. Keim, Ann Arbor, Mich.: We suggested that the tests should be read on the following morning without shaking. However, I noticed that immediately when the tubes were received in the audience, they were shaken; while this does not dissolve the precipitate, it does break it up and make it less perceptible to the naked eye. We are planning further studies with this test, and hope at a later date to add more data on its clinical application.

Dr. Albert Keidel, Baltimore: Whether or not we shall have to change our conceptions of immunity will be told by the future, but it seems today that our original ideas about immunity in parasitic diseases are about to undergo some rather fundamental changes, particularly getting away from the idea of the more or less graphic conception which we carry in our minds of Ehrlich's side-chain theory. We are approaching the chemical solution rather than the biologic

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solution of these theories. The question of strains has a bearing on the problem I presented, but as it is such a controverted point I wish only to say that my attitude toward the existence of strains, the neurologic strain, for example, is not one of great enthusiasm. I think the arguments against the existence of strains are very much more sound and practical than those in favor of them.

Dr. J. E. Moore, Baltimore: In reply to Dr. Lane, I did not attempt to make any very definite comparison with cyanid or other mercurials used intravenously. Cyanid contains by weight about 83 per cent. of mercury as against 32 per cent. for the new drug. The maximum therapeutic dose of cyanid is about 0.02 gm., whereas the therapeutic dose of flumerin is from 0.2 to 0.3 gm. On the basis of mercurial content, that means about seven times as much mercury in flumerin as in cyanid. The therapeutic ratio of both drugs is 1:1. The single curative dose in animals is practically the maximum tolerated dose. In order to cure the disease one has to kill the animal. No experiments have been carried out with node transfer for other mercurials, so far as I know, so that we feel we have a better criterion of cure for flumerin than for other preparations. I am not familiar with any recent literature on the use of cyanid alone. I am familiar with much literature in which cyanid has been used in connection with other drugs, and I feel that such work is absolutely of no value in estimating the worth of cyanid. This drug has been supplied to four or five clinics, notably those of Dr. Fordyce, Dr. Schamberg, Dr. Stokes and Dr. Wile, who I hoped would say something about it. Dr. Schamberg has been particularly interested because of the work he and Dr. Kolmer had done on the mercurials.

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ULCERATING GRANULOMA (GRANULOMA INGUINALE)

HERMAN GOODMAN, B.S., M.D.
NEW YORK

Ulcerating granuloma is also known as granuloma inguinale, ulcerating granuloma of the pudenda, sclerotisizing or sclerosing granuloma of the pudenda, serpiginous ulcerations of the genitalia, granuloma inguinale tropicum, granuloma venerum, groin ulceration, chronic venereal sores and granulomatosis. It is a skin and mucous membrane disease found in the tropic, subtropic and temperate zones. It is an infectious, chronic, indurated, cicatrizing growth on or near the genitals of males and females, with no tendency to glandular involvement or serious impairment of the general health. The majority of the patients are in the period of sexual maturity. Women are said to be more frequently affected than men. The colored races have been thought to have a predisposition to this disease, but a large number of white patients have also been reported.

I have had the opportunity of studying cases of granuloma inguinale in Porto Rico and other islands of the West Indies, and in Panama.[1] Since my return from the tropics, I have also had the opportunity of studying cases of this disease at Bellevue Hospital and at the New York Skin and Cancer Hospital. It was thought that a review of personal experience, both in the tropics and in New York, would be of interest.

TROPICAL CASES

The first case of ulcerating granuloma of the pudenda was in a prostitute, aged 22, who had had the

1. Goodman, Herman: Ulcerating Granuloma of the Pudenda: A Review of the Literature with a Bibliography and Some Observations of the Disease as Seen in Porto Rico, Arch. Dermat. & Syph. 1: 151 (Feb.) 1920.

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disease for nine years. When first seen, lesions of condylomata lata of syphilis surrounded the areas of the granuloma. Antisyphilitic treatment cleared the manifestations of syphilis, but left the other masses unaltered. The lesions occupied the regions in and about the vulva, perineum and anus. They extended into the vagina and into the rectum. The individual lesions were small papillary tumors about the size of a pea. The odor was very offensive. Bacteriologic investigations of material from this patient's lesions (Fig. 1) disclosed a spirochete which corresponded closely to that described by Wise, and later named *Spirochaeta aboriginalis*. This spiral organism varies very much in form and number of turns. As far as I was able to determine, no other organism, especially *Calimatobacterium granulomatis,* was present in smears from tissue of the lesions in this case.

The second patient was a mulatto, aged 32, who had had the lesions for about three years. The process included the anal mucosa, as well as the skin of the femoroscrotal junction, and extended back to encircle the anus. Several individual lesions were present as satellites to the main masses. The appearance of the lesions in this patient compared favorably with those first described by Conyers and Daniels as "lupoid form of so-called groin ulceration."

My third patient was a mulatto girl, aged 17, who had had the lesions for about two years. She showed a series of lesions which involved the posterior fourchette, the posterior vaginal wall and the perineal space. The vagina was involved, and felt distinctly hard. There was a marked lymph stasis. The glans clitoridis was as large as an adult glans penis.

The fourth patient was a discharged white soldier who, several years previously, had been operated on for a small papule on the intergluteal fold. He developed a mild mental disturbance and was placed in a mental hospital for a time. When I first saw him, he presented massive, bright red granulations from the tip of the

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coccyx to the scrotoperineal junction. The opposing anal folds were affected. The border was raised and made up of closely grouped papules covered by a thin grayish membrane and exuding a serous fluid.

Three other patients were seen at Charlotta Amelia, St. Thomas, Virgin Islands.

A patient at the Santo Tomas Hospital, Panama City, was seen after an operation for supposed epithelioma of the penis. The youth of the patient, 23, and the history of the case led me to venture a diagnosis of granuloma inguinale. Dr. Gehringer kindly gave me the only section he had (Fig. 2), and one (Fig. 3) from the extirpated glands. The histopathology corresponded to that of the other cases.

Clinically, the cases seen in the tropics were typical cases as far as tropical experience of others is concerned, for South American authors picture some cases which are almost counterparts of them.

NEW YORK CITY CASES

It did not surprise me to encounter cases of granuloma inguinale in New York City. In my first paper, I had written: "The increasing migrations between continental United States and Porto Rico, with the possibility of transferring the infection, is deemed of sufficient importance to warrant the reporting of the first cases diagnosed on our insular possessions." Further in the paper, I stated: "Quarantine measures should certainly be introduced to prevent the transfer of the infection to our southern ports, either from Porto Rico or from South American countries." Once a source of infection has reached the community, it does not take long for numerous cases to arise, especially as there is a certain predilection for the colored race. It has not been thought worthy of any special note that some of the patients had never left the district of their birth.

I recognized my first New York City case at the New York Skin and Cancer Hospital. Dr. Clifton had

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the case, which for a time was considered oriental sore of the penis, but which, clinically, bacteriologically and therapeutically, was an undoubted granuloma inguinale lesion. Other cases have appeared at this hospital and at Bellevue Hospital.

The penis was the site of the affection in one of our Bellevue Hospital cases, in the service of Dr. Parounagian, and a colored man showed this disease localized to the penis. A colored woman was another patient, and she presented the primary lesion of the disease on the clitoris and prepuce. Another colored woman reported with a large mass in the groin (Fig. 4). It is this type of lesion which warrants more than the others the appellation of granuloma inguinale. Our most recent case is that of a light mulatto girl, aged 19, who came to the clinic with a malodorous crusted saddle-like mass about the clitoris, and a serpiginous papillomatous lesion over the buttock, with a large scar between. She had been operated on at another city institution some years previously. The significant item regarding these two last cases in females was that clinical examination of the present husband in each case disclosed no clinical manifestations of the disease on their genitals. The patient presenting the granuloma inguinale mass had been living with her present spouse for two years. The last girl had been married to her present husband only eight months, and had been pregnant about three months.

The most interesting case of granuloma inguinale I have met is the following, which has already been published as a case report.[2]

A man, white, an American, aged 32, presented a mass of hypertrophic, foul smelling, discharging, red papules and nodules, involving the region of the groins, across the pubes, along the femoroscrotal clefts circumscribing the anus and in the depression between the buttocks and the legs. In this region, the clinical appearance was identical with that pic-

2. This case has already been reported by Parounagian, M. B., and Goodman, Herman: Ulcerating Granuloma (Granuloma Inguinale): A Report of a Rare Example of This Disease in a Syphilitic Patient, Arch. Dermat. & Syph. 5: 597 (May) 1922.

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tured by De Souza Arauja[3] in a South American case. But in addition, the patient (who had never left New York City) presented similar lesions of the lips and the side of the neck. As far as I know, this is the second case of labial involvement of this disease. The first was reported by Sequeira,[4] in whose patient a genital lesion of ulcerating granuloma was also present. The tongue of my patient presented a smooth atrophy, such as only occurs in syphilis, and the serologic course justified a diagnosis of syphilitic glossitis.

HISTOLOGIC AND BACTERIOLOGIC SUMMARY

Histopathologic studies of cases seen in the tropics or in New York City have disclosed no specific change, but the elongated papillae and interpapillary processes have been present, as would be expected from the clinical appearance of the lesions, with collections of fibroblasts, polymorphonuclear leukocytes, and round cells. There is nothing present to indicate the presence of epithelioma, tuberculosis or syphilis. It would as a general thing be impossible to make a diagnosis from the appearance of the section alone, although it might be suggested.

In the tropical cases and in those seen in New York City, tissue smears were made. In my experience, it is important to get material for bacteriologic study from tissue not contaminated by surface organisms. Under a local anesthetic, a portion of the active margin is well cleansed and removed. The portion is then trimmed so that only deep tissue is made available. This is washed in saline solution, and smears are made by expressing tissue juice from the block.

In each of the cases except the first and the last, organisms of the *Calimatobacterium granulomatis* type were disclosed. The organisms were within large mononuclear cells grouped about one side of the nucleus. Each germ was inside a capsule. I have also seen extracellular organisms which are assumed by some to be immature forms. It has been difficult to

3. De Souza Arauja: Granuloma Venereo, Trabalho di Instituto Oswaldo Cruz, printed privately in Portuguese, 1917.
4. Sequeira: Ulcerating Granuloma of the Pudenda, Brit. J. Dermat. & Syph. **20**: 91, 1908; Proc. Roy. Soc. Med., Dermat. Sec. **1**: 57, 92, 1908.

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get satisfactory pure cultures, and, in my experience, it has seemed unlikely that the true organism, as seen within the large mononuclear cell, is the organism cultivated. It has been claimed, for example, that the cultural characteristics of the organism of granuloma inguinale place it in the Friedländer or *Bacillus mucosus-capsulatus* group. However, every attempt at cross agglutination or cross precipitation with known Friedländer organisms has failed.

It has been impossible from cultures of the organism grown from granuloma inguinale cases always to secure positive animal inoculations. Although some authors have found the organism grown from their cases to be pathogenic on intraperitoneal injection, mice so injected have also been unaffected, in my experience.

Attempts at experimental autoinoculation have failed in my own experience and in that of others.

The original conception that the organism named *Calimatobacterium granulomatis* (Fig. 5) was a Leishman-Donovan body has assumed less importance with time. Still, one cannot be certain, and until absolute proof is forthcoming to the contrary one may consider such a conception as a possible one. In this connection, it is interesting to speculate as to the method of transference of the disease. Although in Porto Rico I had the opportunity of examining more than 1,100 active prostitutes, but two examples of this disease were encountered among them. No soldier among the 18,000 trained at Camp Las Casas, Porto Rico, had the disease, the two male patients being a civilian and a discharged soldier of the peace time Porto Rican regiment, respectively. As mentioned earlier, two recent women patients with this disease were both married, yet examinations of the respective husbands revealed no lesions. The possibility of an intermediate host must also be borne in mind, especially in the light of the existence of such an intermediate host in other protozoan diseases. From its location, should there be

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Fig. 1.—Spirochaeta aboriginalis.

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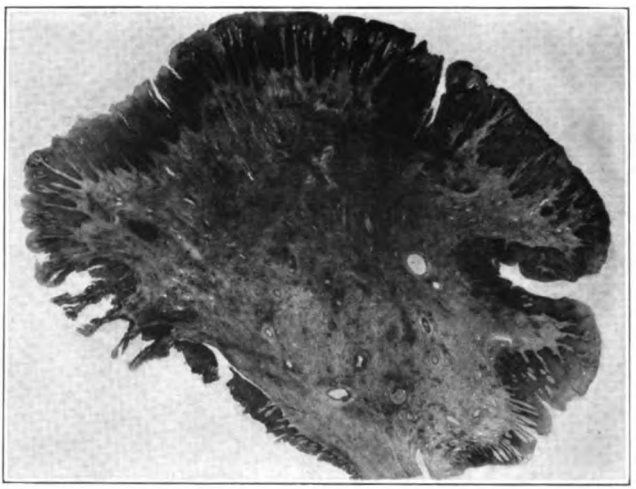

Fig. 2.—Granuloma inguinale: section from patient at Saint Tomas Hospital, Panama Republic.

Fig. 3.—Section of gland removed from patient. The reaction was only that of chronic inflammation. There was no specific change.

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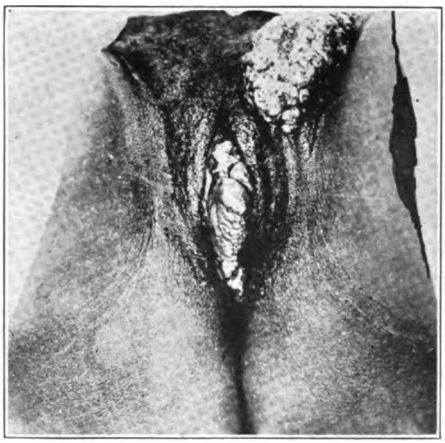

Fig. 4.—Granuloma inguinale: lesions in a colored woman.

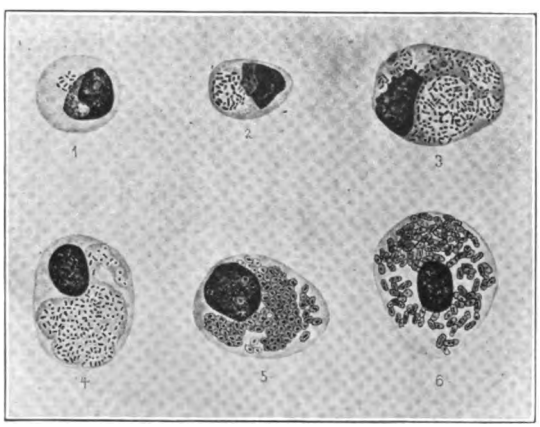

Fig. 5.—Calimatobacterium granulomatis: development of organism (from colored plate of De Souza Arauja).

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an intermediate animal host for granuloma inguinale, *Pediculus pubis* would be most likely, yet I must report that the diagnosis of pediculosis pubis was made in only twenty-four cases among three regiments of Porto Rican soldiers.

RHINOSCLEROMA AND GRANULOMA INGUINALE

Although clinically and pathologically very dissimilar, rhinoscleroma and granuloma inguinale have been thought to be somewhat related by reason of the morphologic resemblance of the organisms encountered in some cases of each. Rhinoscleroma is supposedly due to a bacillus, gram-negative, easily grown, and of the Friedländer or *B. mucosus-capsulatus* group. This is the link between the two diseases, and is the only link, and a weak one. Rhinoscleroma has a predilection for the respiratory tract; its histology is pathognomonic and is characterized by the presence of three essentials: (1) the foam cells, or nucleated dropsical cells of Mikulicz; (2) the von Frisch bacilli, and (3) the hyalinized cells of Unna. All of these are lacking in granuloma inguinale, for it is admittedly difficult, if not impossible, to demonstrate the organisms in the tissue of granuloma inguinale. A more complete analysis of these two diseases will be published at another time.

LEISHMANIASIS AND GRANULOMA INGUINALE

It has already been mentioned that there is some resemblance between granuloma inguinale and oriental sore in the morphology of the organisms, but certainly in no other way. The biology of these morphologically similar organisms must be very different, as can readily be recognized if one recalls the ease of contagion in oriental sore and the nature of the contagion in granuloma inguinale. Morphologic resemblance must be also admitted with the organisms of tropical ulcer, and to kala-azar. Espundia, or naso-oral leishmaniasis, and gangosa are other tropical diseases which seem to fit in between granuloma inguinale and rhinoscleroma.

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SYPHILIS AND GRANULOMA INGUINALE

Clinically, a number of diseases may require differentiation from granuloma inguinale. Ordinary condylomas of syphilis may simulate the condylomatous type of granuloma inguinale. Elephantiasis vulvae of syphilis may assume the appearance of the lymphatic stasis type of the other disease. Gummatous destructions of the external genitalia are not so likely to be confusing, since, despite the name of ulcerating granuloma, this disease is not so destructive as might be implied.

There are, however, many exceptions to the conception that granuloma inguinale is syphilitic or the result of a syphilitic infection, although it is admitted that the two diseases may be concomitant. As mentioned earlier, my first patient had lesions of condylomata lata of syphilis about the area of granuloma inguinale, and other patients had positive Wassermann reactions with no clinical manifestations of syphilis. Intensive and persistent treatment with arsphenamin and mercury made no therapeutic impression on the lesions of granuloma inguinale. In other cases, equally extensive, there had been repeated negative Wassermann reactions. Although spirochetes have been found in a number of cases of granuloma inguinale, the organism has not been found in every case, as might be expected if it were causative. The histology of the lesion is not that of syphilis. Contagion is a much more remote possibility, although it must be conceded that, if comparison in this respect with the gumma lesion of syphilis is insisted on, this feature cannot be used in differentiating the two diseases. However, it is not logical to consider granuloma inguinale a tertiary manifestation, when it is found concomitantly with secondary manifestations in some patients.

YAWS AND GRANULOMA INGUINALE

I can find no weight of evidence that granuloma inguinale is a tertiary yaw lesion, although I have had some tropical experience with frambesia tropica. Prac-

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tically the same objections to the theory that there is a relationship would hold true in the case of yaws and granuloma inguinale, as in syphilis and granuloma inguinale.

NEW GROWTH (NEOPLASM)

Epithelioma and carcinoma of the regions ordinarily affected by granuloma inguinale may look like it, and indeed one of the patients had had the growth excised under the diagnosis of malignant growth. Another patient was thought, under clinical examination, to have granuloma inguinale, but pathologic examination definitely established the diagnosis of epithelioma. This patient, in addition, on bacteriologic examination, showed organisms similar to those of Vincent's angina. Some cases of dermatitis vegetans might be confused with granuloma inguinale.

TREATMENT

The treatment of granuloma inguinale with antimony and potassium tartrate, or tartar emetic, has given uniformly good results wherever tried. Intravenously, it is ordinarily given in dilution of 1 : 100. I have always had the solution prepared in distilled or double distilled water, cold, as it appeared that heat decomposed the tartar emetic immediately. Other workers have sterilized their solution by autoclave without ill effects. The dose is 5 c.c. of the 1 : 100 solution every other day, increased by 1 or 2 c.c., until 12 c.c. every other day is injected. Recurrences are common unless treatment is carried on long after the lesions have disappeared.

SUMMARY

Tropical and temperate zone experience with ulcerating granuloma or granuloma inguinale are reviewed. The various clinical types of this disease, are ulcerative, papillomatous, psuedo-elephantatic, and condylomatous. Examples of the two contending bacteriologic causes are cited; namely, a case from which *Spirochaeta aboriginalis* was demonstrated and

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other cases from which *Calimatobacterium granulomatis* was isolated. An example of involvement of the lips and side of the neck is summarized. A résumé of the histologic and bacteriologic features of granuloma inguinale is given, with a discussion of specificity of the organisms, animal experiments and autoinoculation.

Comparative features of granuloma inguinale and rhinoscleroma, leishmaniasis, syphilis, yaws and neoplasms are reviewed and analyzed. The discussion of rhinoscleroma has been especially full in view of the suggestion that organisms both from granuloma inguinale and from rhinoscleroma belong to the Friedländer or *B. mucosus-capsulatus* group of organisms.

The treatment and prognosis are briefly touched on. Some of my work along the lines of a specific fixation test with antigen prepared from tissue taken from cases of granuloma inguinale is not far enough advanced for more extended mention. The photographs and photomicrographs are from the collections of Goodman, and Parounagian and Goodman.

15 Central Park West.

ADDITIONAL REFERENCES

In addition to the references given in my earlier paper,[1] the following will be of interest:

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ABSTRACT OF DISCUSSION

Dr. Joseph Grindon, St. Louis: In 1913, I reported three cases showing some of the features described by Dr. Goodman. In one case neither Donovan bodies nor spirochetes were found, although I felt that there must be a specific organism. Crocker considered it a chronic pus infection, thus ranging it with granuloma pyogenicum. This theory I cannot accept, on account of the rarity of the condition. If it were due to a frequently encountered cause, the result would be frequent. Here, on the contrary, are rare cases, which at the same time show a close adherence to type, a "pattern disease," a terse expression often used by Dr. Hardaway. My researches, cultural and animal, yielded negative results. I believe that, in the minds of some of those who have not seen the disease, there lurks a suspicion of syphilis or chancroids, or something else. Those of us who practice in large cities see extensive chancroids, often in old syphilitics, extending over the groins and down into the perineum. In these cases, the leading feature is ulceration; but not so in inguinal granuloma, and that is why the term "ulcerating granuloma of the pudenda" is objectionable. The disease follows closely Manson's original description. A little nodule in the groin grows slowly, and ultimately becomes a superficial ulceration. It spreads peripherally, and also forms new lesions by auto-infection, through apposition. As it extends, there forms and progresses a peculiar cicatrix, dense, hard to the touch, with the appearance of a hypertrophied scar or keloid, and at the periphery a spreading mass of nodules, with occasional island lesions. The leading features are the nodules, the superficial ulceration and the cicatrization. There is a false appearance of deep ulceration in the folds between the thighs and the scrotum. There you find a deep cleft running along a low ridge, simulating a deep ulcer by the infolding of the affected surface. At the top, the ridge is sharply cut down toward the fold, but in the opposite direction it gradually slopes down toward the border of the diseased area. The disease possesses clinical

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characters entirely distinct from those of syphilis, chancroid, lupus or epithelioma.

Dr. A. J. Markley, Denver: I should like to place on record a typical case of granuloma inguinale seen in Hawaii, where I think no other cases have been reported. This case was in a negro soldier. It was a penile lesion, which for many months defied diagnosis and treatment, and not until there came to my notice a report of the work on granuloma inguinale done by some South American authors did I have any conception of the character of the disease. Then smears gave the typical picture of granuloma inguinale, and the intravenous use of tartar emetic resulted in absolute cure. There had never been a case of this sort reported in Hawaii.

Dr. Jeffrey C. Michael, Houston, Texas: This disease is seen not infrequently in Houston, where there is a rather large negro attendance at the clinic. Four cases of chronic ulcers of the leg have been of interest. Three of the patients were negroes; the other, a white boy. The oldest patient was 24 years of age, the youngest 16. The duration varied from six months to seven years. All cases followed traumatism, slowly spreading until in the case of longest duration a large part of the cutaneous surface of the right leg was involved. The cause could not be determined, and the lesions were resistant to treatment of all sorts, including antisyphilitic treatment. All the patients had negative Wassermann reactions. About this time Lynch reported two cases of chronic ulceration in which Donovan's bodies could not be found, but which responded well to tartar emetic given intravenously. We used this treatment in two of the cases, and they cleared up in a manner which suggested that tartar emetic had something to do with it. The effect of treatment in these patients indicates a probable etiologic connection with granuloma inguinale.

Dr. William Litterer, Nashville, Tenn.: This condition is not so rare as we are led to believe. A similar condition prevails among the negroes in the South, especially in females. Within the past year, I have seen five cases in the Vanderbilt Hospital and the Nashville City Hospital. Three of these cases are now under observation. The Donovan bodies have been demonstrated and treatment by tartar emetic intravenously has brought wonderful results. All of these cases have been associated with some venereal infection. Practically all of them have had either a syphilitic or a gonorrheal infection. Three patients gave a four plus Wassermann reaction. Antisyphilitic treatment was given until a negative Wassermann reaction was obtained, but the condition did not yield until tartar emetic was administered, and then the lesions cleared up promptly.

Dr. Jesse B. Shelmire, Dallas, Texas: I can recall seeing several cases with similar conditions in the Charity Hospital of New Orleans during 1881-1883, in which various treatments

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were given, but few, if any, patients were cured. In those days, these cases were diagnosed as chronic chancroids, but I believe now that most, if not all, were cases of granuloma inguinale. Three years ago, I referred a case to one of our surgeons. He tried various methods of treatment without success, after which the patient drifted to Hot Springs. He returned to Dallas last December with this condition involving the inner surfaces of the thighs, the entire penis and the abdomen half way to the umbilicus. The lower lip was involved, beginning six months before. The affection began as a papule on the penis seven years ago, some time after a visit to South America. We were then able to make the correct diagnosis, finding the Donovan bodies. He was placed on the tartar emetic treatment and at present is practically well.

Dr. Harold N. Cole, Cleveland: In the eight cases of this disease that I have seen we were not able to make the diagnosis with the microscope in all. I think there was no question about the clinical diagnosis, and we went ahead and treated them. If you have one of these cases which does not react to other treatment, you may be sure that it is of this type. The action of the drug is almost immediate. One word of caution, however: we found that the kidneys must be watched very carefully. In one case we set up quite a high degree of nephritis.

Dr. Earl D. Crutchfield, Galveston, Texas: This disease has a more protean character than the cases we have seen reported in the literature in the last four or five years. The first case I saw was that of the patient whose picture appeared in Dr. Sutton's textbook. We regarded that as a type of granuloma and were considering typical granuloma inguinale. Four or five cases had been seen in Galveston in the past three or four years which were very similar to those seen in the last few months. We have been able to demonstrate Donovan bodies in ulcers which had existed three or four years. One case was that of an orderly in the University Hospital, which we had diagnosed as chronic chancroid; but we were able to demonstrate the Donovan bodies two or three months ago, and it cleared up very rapidly with tartar emetic. In all of these cases, I have demonstrated the organism of Donovan.

Dr. Herman Goodman, New York: Tartar emetic has been mentioned as a specific, but few men have attempted to dilate on the preparation of the drug for intravenous injection. It was suggested to me that in order to have the tartar emetic act specifically, the solution must be prepared in the cold, using doubly distilled water and chemically pure antimony potassium tartrate. At a symposium in New York, I was surprised to hear mentioned the use of the autoclave or boiling of the solution before use and no untoward results, It had been my impression that such preparation would break up the double salt, and that there would be a reaction. The

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drug is ordinarily given in doses of 2 c.c. of the 1:100 solution, increasing the dose to 10 or 12 c.c. by adding 2 c.c. to each preceding dose. If the dose is given too rapidly, the patient complains of pain which may extend to the shoulder of the arm used for injection. The pain is so marked after a dosage of 10 or 12 c.c. is reached that the patient often discontinues the treatment. One should keep in mind also that if one does not persist in the treatment, the lesions of the disease will recur. If one finds that ten or twelve doses have cleared the lesions, the patient should be urged to have another course of this number of treatments. With insufficient treatment, recurrences may be repeated a number of times, because the type of patient afflicted with this disease ordinarily is difficult to keep under treatment after the symptoms have disappeared. I should like to suggest the use of a complement fixation test with tissue from patients as the source of the antigen. There is no fixed clinical type of granuloma inguinale. Individual cases fit in because we find the organism said to cause the disease, although the free use of the term "Donovan body" is certainly not justified without reservations.

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SPOROTRICHOSIS

FRANK W. CREGOR, M.D.
INDIANAPOLIS

Sporotrichosis is more frequently encountered than any of the other dermatomycoses. The disease is so constantly confined to the cutaneous and subcutaneous tissues that we seem not to have sufficiently acquainted ourselves with its protean character. It may attack many other tissues of the body, and manifest itself in a manner so far removed from the usual clinical picture that it is only by the most careful observation, with the aid of thorough laboratory investigation, that we are able to cope with it.

It is because of encountering a case, which clinically was simple enough, yet which presented some of these important though rare involvements, that I make this report. At the same time, I would like to call attention to the variable manifestations that may appear, with the hope of stimulating the profession to a more thorough investigation of some of these infections, which do not seem to fit any particular entity, yet may have *Sporotrichum schencki* for an etiologic factor.

Sporotrichosis has been recognized as an entity for the last twenty-four years, or since Schenck first described the malady, and discovered and, with the aid of Erwin F. Smith, classified the causative organism. Dr. A. W. Brayton of Indianapolis reported the second case. Following closely came the work of Hektoen and Perkins, Hyde and Davis in America, de Beurmann and his associates in France, Arndt in Germany, Kren and Schramick in Austria, and Adamson and Walker in England. These reports, which were published during a period of about ten years following Schenck's

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contribution, served to establish sporotrichosis in the medical literature. Since that time, or during the second decade in the life of the disease as a recognized entity, many interesting contributions have been made, especially to the American literature, by Mewborn, Sutton, Meyer, Blaisdell, Shelmire, Trimble and Shaw, Hamburger, Raney and Carey, Stelwagon, Newman, Ravogli, Soloman, Ormsby and Lane. In addition, reports that have found their way into the literature indicate that the disease is encountered all over the world.

The clinical picture of sporotrichosis is very constant —so constant that it has had for its effect the dimming of our vision as to its protean nature. The textbooks make only a mild mention of it, and those making contributions to the American literature do not seem to have encountered it except in very few instances. It would seem that what we know of its variable manifestations we owe, in the main at least, to the French. It is because the American literature contains little or nothing concerning the involvement of tendon sheaths, periosteum and bone that I am desirous of bringing this case to attention.

Usually, there is a trivial trauma. After a time, it is discovered, the injured part has not responded normally, but becomes swollen, livid or bluish in appearance, takes on a shape in keeping with the nature of the injury, and is found discharging a syrup-like secretion, which may be tinged with pus and blood. The appearance of this initial lesion, or chancre as it is termed by some, may be expected to have been influenced by the application of various domestic remedies, consisting of everything from poultices to caustics. It may be encountered anywhere on the body, but most frequently on the hands, for the reason that the hands are most exposed to injury. By the time the stubborn nature of the sore has caused alarm to the host, the secondary lesions will have begun to appear. A nodule, usually

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in a direction toward the trunk, is observed, located deep in the subcutaneous tissues; it imparts a firm feeling to the touch, and may be expected to be moderately tender. If a still greater time has elapsed, other lesions may have developed, the newer ones following in a direction toward the trunk, until there may be observed many nodular swellings, extending up the arm in chainlike formation, and presenting different stages of progression or regression. There may be observed firm hard nodules covered by a pinkish skin, others which have softened, and others which are discharging their contents, consisting of a syrupy fluid, as before mentioned. My observations have been that there are usually from four to six such lesions, extending from the injury on the hand to the elbow. The patients experience a feeling of well being, remain ambulatory, have little or no elevation of temperature, and, aside from the inconvenience and apprehension, appear quite well. Such may be said to be a fair description of a typical case of sporotrichosis, reports of which, as has been mentioned, have been voluminous.

The disease may affect parent and child, one such case coming under my own observation; it has been reported to have affected as many as three children in one family.

It may suggest a latent syphilis, as it almost always does, to those who are not especially familiar with skin lesions; or, at the site of the initial lesion, or chancre, it may present the clinical appearance of a tuberculosis verrucosa cutis or of a blastomycosis or of both, as it did in my case.

The disease may attack the tendon sheaths, periosteum and bone. In my case, there is a history of a fracture involving these structures, occurring about fourteen years previous to this infection. I have the feeling that changes in the course of the lymph stream, incidental to the fracture and repair, may have directed the infection into the deeper structures, and thereby

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caused the involvement of tendon sheaths, periosteum and bone, which otherwise might not have occurred.

Sporotrichosis may also infect the blood stream and produce a septicemia and a generalized gummatous process of the skin, together with gummatous lesions of the liver and other viscera, and *Sporotrichum* may be recovered from the blood stream.

It may be associated with tuberculosis, and may attack structures such as the pharynx, larynx, trachea and mucous membrane of the mouth, along with tuberculosis.

It would seem, experimentally at least, that when infection has found its way directly into the blood stream, dissemination may be so rapid that the host is overcome before Nature has had time to organize a defense. Too, it is probable that when the sporothrix has found lodgment in a person suffering from tuberculosis of much moment, the body defense has been so exhausted by the tuberculous infection that it is unable to put up a strong fight against *Sporotrichum*.

In the type of infection usually encountered, namely, the subcutaneous lymph space variety, the infection has slow progress, which gives the normal body defense an opportunity to organize for resistance. This would seem to suggest itself as a result of the power of the patient's blood to agglutinate the spores of *Sporotrichum*.

Experimentally, sporotrichosis has been produced by feeding animals on infected foods, and has been produced in the offspring by infecting mothers in the pregnant state. By blood stream inoculations, it has produced a rapid dissemination, metastasis and death. At postmortem examination, the thoracic and abdominal viscera have been found involved in a tuberculoid and syphiloid granulomatous inflammatory process. It may interfere with development, by producing dystrophies and arthropathies; nevertheless, the animals have remained mentally normal.

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The difference in *Sporotrichum* as discovered by Schenck in 1898, and as later described by de Beurmann and his associates, would seem not greater than that of any vegetation growing in changed climatic environment, and, in my judgment, should not concern us.

The organism grows readily on the simpler mediums; for the most part, however, in the presence of secondary infection it may not, as it did not in my case and in another case of a similar character. It may be found microscopically in the pus, as it was in my case. But it would seem, from the experience of others, that this is rarely true. In the other case mentioned, which was of a similar character, the culture growth failed, and the diagnosis was made by the agglutination test. The diagnosis later was further confirmed by successfully cultivating *Sporotrichum* from the secretions, after sufficient time had elapsed to clear out the secondary infection.

We did not have growing, at this time, any cultures of *Sporotrichum,* so the agglutination test was not employed. As the clinical diagnosis had been amply confirmed by finding the organism in the pus, I felt quite content to proceed with the treatment.

The histopathology presents a lymph connective tissue, or the so-called syphiloid zone, and an epithelioid or tuberculoid one, with a suppurative area. With the means now at our command, the diagnosis of sporotrichosis has been rendered simple. In the cases usually observed, the clinical picture is quite sufficient. I feel sure, however, that if we study our obscure cases carefully, especially with the view of ruling out sporotrichosis, we shall encounter it more frequently. Examination of the secretions for *Sporotrichum,* cultivating the organism, and the application of the agglutination test of Widal and Abrami, would serve to rule it out. This agglutination test is not specific as against some of the other mycoses, except as to dilu-

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tions and time; while the spores agglutinate, the myecelia do not. It has been found positive one year after cure, and has been found negative five years after a cure.

The prognosis in the uncomplicated cases is very good.

The treatment by iodids internally, and the application locally of dilute iodin potassium iodid solution are specific. There seems to be no potential danger of disseminating the organism by absorbing the granulomatous tissues.

REPORT OF CASE

History.—F. T., a man, aged 33, American, married, teamster, referred to me by Dr. John H. Oliver of Indianapolis, Jan. 24, 1921, complained of boils and swelling of the right hand and forearm for the last fourteen months. The patient was the father of three healthy children. He had had measles, whooping cough, scarlet fever and pneumonia, with good recovery. He had suffered a fracture of the right wrist fourteen years previous to this time, and had been a patient in an institution for the insane, where he had been regarded as having dementia praecox of the paranoid form. He escaped from the institution, and, as he seemed to be adjusting himself fairly well on the outside, he had not been disturbed. There had been an abscess on the ring finger of the right hand, which had healed without treatment.

During November, 1920, or fourteen months previous to this time, he had scraped the skin on the back of his right hand while working as a teamster. This injury had refused to heal, and discrete swellings had appeared along the ulnar side of the arm, which had broken down and discharged, leaving contracted scars. The hand became swollen. The ring and little fingers began to draw down, and the use of the hand was gradually lost.

The family history was negative, with the exception that a distant cousin had had bone tuberculosis.

Physical Examination.—The patient was well built. He was poorly developed mentally. The abdomen, chest and nerve reflexes were normal. There were 13,500 leukocytes. The Pirquet reaction was positive. The ring and little fingers on the right hand were drawn down and fixed so that any extension was impossible. The wrist and body of the right hand were swollen and thickened. There were four contracted scars along the ulnar side of the hand. There was a similar, but larger, lesion on the flexor surface of the

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Fig. 1.—Appearance of arm in case reported, in which tendon sheaths, periosteum and bone were involved, with thickening of tissues about the hand and wrist.

Fig. 2.—Initial lesion on dorsal surface of hand and arm, showing resemblance to blastomycosis and to tuberculosis verrucosa cutis.

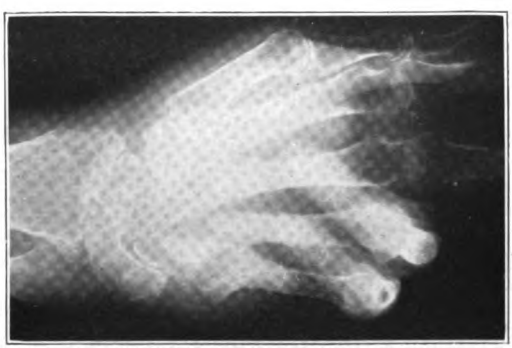

Fig. 3.—Destruction of head of fourth carpal, and erosive, destructive process involving metacarpal bones.

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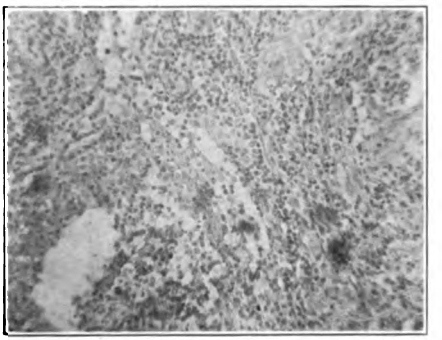

Fig. 4.—Syphiloid outer zone of gumma.

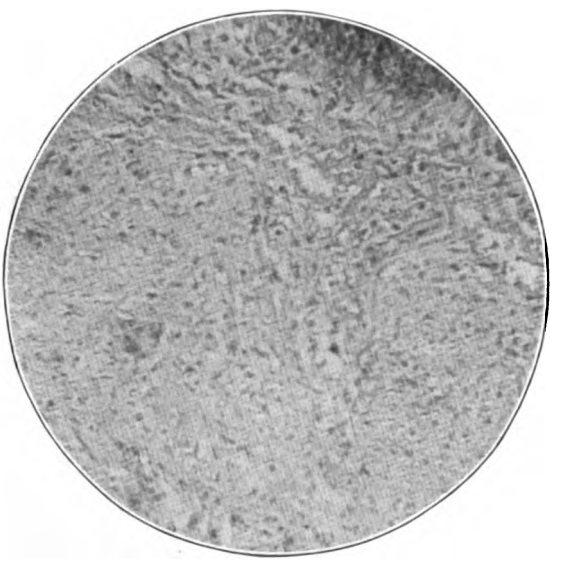

Fig. 5.—Tuberculoid inner zone of gumma.

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radial side of the wrist. On the dorsal surface of the same hand there was an irregular eroded surface, about 8 by 5 cm., composed of sinus openings, pus pockets, and verrucose formations.

This lesion had the appearance of blastomycosis and of tuberculosis verrucosa cutis. A probe pressed into the sinus openings passed deeply into the tissues of the hand.

In the laboratory, culture tubes were inoculated, smears examined and histopathologic studies made by Dr. V. H. Moon of the department of pathology of the Indiana University School of Medicine. In the pus smears, stained with methylene blue, were found pus cells, débris and a number of bacterial species, among which were cocci, and diphtheroid and other bacilli, such as are found as saphrophytes in open skin lesions.

Smears stained with carbolfuchsin contained no acid-fast bacilli.

Pus examined under coverslips after digestion with 10 per cent. potassium hydroxid contained clear, refractile, oval forms, elongated sausage-like forms, and navicular and short filamentous forms. These were from 3 to 4 microns in diameter, and from 5 to 7 microns in length. The diagnosis from examination of the pus was sporotrichosis. Cultures from the pus were abundantly overgrown by the bacterial species present. No pure culture of *Sporothrix* was obtained.

Histopathology.—The epithelium and papillary processes of the corium were not altered; except at the margin of the ulcer, the epithelial cells were moderately edematous. The dermis was markedly infiltrated with large mononuclear cells, plasma cells and lymphocytes. Very few polymorphonuclear cells were seen. The cellular infiltration was particularly abundant about the sweat glands and about the vascular structures. There was an evidence of a proliferation of fibrous tissues. The sides and floor of the ulcer consisted of a granulomatous proliferation of a tuberculoid character, densely infiltrated with cells. Large epithelioid cells having two or more nuclei were seen in this area, and a few were found having eight or more nuclei. These giant cells were not so large as those found in tuberculosis, nor were their nuclei placed peripherally. Distinct, small, round, granulomatous areas were present, which resembled miliary tuberculosis somewhat, but these consisted entirely of newly formed fibrous tissue and large mononuclear and multinuclear cells. None of these had caseous or necrotic centers.

Roentgen-ray examination by Dr. Ralph L. Locery of the Indianapolis City Hospital revealed periosteal involvement of the head of the radius and ulna, all of the carpal and metacarpal bones, and a destructive osteitis involving the third and the fourth metacarpal, and some of the carpal bones.

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We failed to get a satisfactory culture growth, our mistake being in taking pus from a discharging sinus. I feel sure that had we inoculated our mediums from the contents of the lesion, which was located on the flexor surface of the wrist over the head of the radius, we would have had better success.

Treatment and Result.—Iodids were given internally, and iodin potassium iodid solutions were applied locally. The patient's heart rate was 165 when the dose had been increased to 45 grains (3 gm.) of the iodids, and it returned to normal when the dose was reduced to 30 grains (2 gm.).

The man left the hospital, March 23, fifty-eight days after he was admitted, with all lesions healed.

725 Hume-Mansur Building.

ABSTRACT OF DISCUSSION

Dr. Richard L. Sutton, Kansas City, Mo.: Sporotrichosis is undoubtedly a fairly common disorder in the Middle West, and in late years many cases are being recognized that formerly escaped detection. I have seen probably thirty cases during the last twelve years. Virtually all of my cases have been of the type shown by Dr. Cregor in his first three, with the earliest lesion on the hand or foot, the abscesses extending upward, along the limb. In none of our cases did we succeed in recovering the organism from the lesion, although, as a rule, our cultures were positive. The disease is one of the agricultural districts, the organism being a not uncommon one in straw and dry vegetable matter. Dr. Cregor's last case was particularly interesting, as the tubercular and gummatous types, while far from rare in France, are seldom encountered in this country. I can recall but one case, that reported by Eisenstaedt. I must agree with Dr. Cregor that after an exhausive study of the organism I hold the same view as Castellani, and Meyer and Aird, that many, if not all, of the numerous French varieties belong in the same category, that it is both useless and confusing to endeavor to separate them into forty-nine different classes. The disease usually responds promptly to iodin medication, possibly supplemented by roentgen rays, and, as a rule, operative intervention is contraindicated.

Dr. J. M. King, Nashville, Tenn.: I enjoyed the paper very much and consider it a straightforward statement of the case. For several years I have been looking for cases of sporotrichosis, and I think that last week I was rewarded with one. A man of about 70 stuck a splinter in his hand last November. He removed the splinter, and to his surprise nodules developed up his arm subcutaneously to within 3 inches of the axilla. His physician treated him with antiseptic applications without any success. The patient was referred to me by Dr. Sayers of Nashville. When I first looked at

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him I said: "There is a case of sporotrichosis." All of these lesions had been opened, and they contained sinuses opening from one to the other. Dr. Spitz made the cultures for me. He found the mycelium in the smear. I opened the other lesions and got out the typical fluid for other cultures, from which we may get more positive results. Since this case was reported, Dr. Spitz has found the sporothrix in the cultures.

Dr. Everett S. Lain, Oklahoma City: I do not know whether this disease is more common with us, but we certainly see more in our section of the country. I think that the reason, perhaps, Dr. Sutton is not seeing so many cases nowadays is that the disease has been so well described by himself and others that the general practitioners are recognizing it and do not need a dermatologist to make the diagnosis. Even hospital interns now recognize sporotrichosis almost on first sight. It usually yields rapidly to iodid treatment. However, one of my patients came back one year later with a recurrence in the original site. He had been given the iodids but no roentgen therapy. Our previous patients had been given both roentgen rays and iodids.

Dr. John H. King, Nashville, Tenn.: I, like Dr. Lain, think that there are many more cases of sporotrichosis in our section of the country than are reported. One point that Meyer noted was that it could be contracted from an equine strain, and he himself contracted the disease from an equine strain, working in his own laboratory. That was particularly so in Pennsylvania, where 150 cases were reported within a few years, yet only two cases occurred among veterinarians and others working on these animals. Another point is the combination of potassium iodid and roentgen rays. While we all feel that potassium iodid is a specific in sporotrichosis, I feel that these advanced or deep cases, such as Dr. Cregor has reported, may be greatly benefited by the roentgen rays. For the superficial treatment I feel that we should use a ray with very slight filtration, while for the deeper lesions we should use a heavier ray with a more or less massive dose. In the case of a boy last year, I feel that his recovery was greatly hastened by the roentgen rays.

Dr. Frank W. Cregor, Indianapolis: In the treatment of the mother and the boy, we attempted to investigate these particular conditions. Dr. Obershimer concluded that the cases developed during the harvesting of the buckwheat, and he offers this as being something that has a tendency to harbor this organism. I cannot see the efficacy of the employment of the roentgen ray in these cases. There is evidently some symbiosis between this organism and others that "live in the shadow," which seemed to succumb when the organisms are destroyed, as they are destroyed by the iodids. In the cases that I have had I have not employed the roentgen ray, and I have never felt the need of it.

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LOCAL BLASTOMYCOSIS

REPORT OF CASE

MARCUS HAASE, M.D.

E. R. HALL, M.D.

AND

C. H. MARSHALL, M.D.

MEMPHIS, TENN.

Since the first description of blastomycetic dermatitis, in 1894, a great number of dermal and systemic cases have been reported, so that the condition is now generally recognized, and further reports of such cases would be mere repetition and scarcely warranted. However, in reviewing the literature, we could find but few cases in which the disease was localized in some viscera or bony structure. In 1907, Brewer and Wood [1] reported a case of blastomycosis of the spine, in the region of the third dorsal vertebra, without any other manifestation of the disease. Campbell,[2] in 1909, studied a case of blastomycotic osteomyelitis of the right tibia, following a lesion on the skin of the ankle, but having no symptoms referable to the lungs or other organs. Denis,[3] in 1918, reported a case of primary blastomycosis of the larynx, which remained localized for several months, but did not respond to treatment, the lungs, later, becoming involved. Although, we have searched the literature carefully, we have not found any other cases of local blastomycosis other than of the skin. However, we feel that there are many more such cases, which have either not been reported or not recognized.

1. Brewer, G. E., and Wood, F. C.: Ann. Surg. **48**: 889, 1908.
2. Campbell, J. L.: Atlanta J.-Rec. Med. **12**: 308, 1909.
3. Denis, F. L.: Ann. Otol., Rhinol. & Laryngol. **27**: 572, 1918.

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REPORT OF CASE

A negro man, aged 78, who, previous to September, 1921, had been under the observation of one of us (M. H.) for seven years, with blastomycosis of the neck and face, stated that the skin condition had been present five years before he sought aid. Under potassium iodid therapy, the lesions healed; but during frequent long absences from observation, new lesions appeared about the old scars. However, the patient remained in apparent good health and the skin condition seemed to cause him but little discomfort.

In September, 1921, he came to the university clinic because of a swollen left testicle. The swelling had developed about three weeks previously; and the mass in the left scrotum was three or four times the normal size of the testicle and epididymis. It was impossible to outline the testicle and epididymis, owing to the thickened scrotum and the inflammatory process about the mass. The lower portion of the mass was adherent to the scrotal wall. There was some fluctuation posteriorly, but very little pain on pressure. The vas deferens was large but not nodular. On consultation with the surgeons, it was thought advisable to remove the organ, they believing it to be malignant or tuberculous. On removal, the testicle itself was about normal size and consistency, although the tunica vaginalis was thickened. The epididymis, on the other hand, was several times the normal size, soft, and joined to the scrotum by thick adhesions.

Microscopically, no pathologic condition was found in the body of the testicle, although grossly the tissue had a peculiar, yellowish-brown discoloration. On cutting into the epididymus, a considerable amount of yellow pus was found. Cultures of this material grew typical colonies of blastomycetes. Microscopically, the tissue was invaded by granulomatous tissue containing many plasma cells and leukocytes, mostly polymorphonuclear and giant cells of the Langhans type. Typical miliary abscesses were present, in and about which the blastomycetes were found. These organisms were also found in the giant cells.

The patient made an uneventful recovery from the operation. There was no other positive evidence of the disease in other viscera.

During the seven years that the patient was under observation, he entered the hospital four times. Twice, he was admitted for surgical removal of skin lesions, and at each of these times the physical and laboratory findings were entirely negative. He was admitted the third time for the removal of the testicle, and has been admitted once since for observation. At each of these visits to the hospital, a systematic search was made for any other pathologic condition in the body. Again, the physical and laboratory findings were normal. Roentgenograms of the chest revealed some peribronchial and interstitial fibrosis; but there was no cough,

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expectoration or other symptoms referable to the lungs. The second roentgenograms did not differ from the first, and apparently the process was inactive and of long standing. At the present time, the patient is well nourished, strong, and very active for a man of his age.

COMMENT

Metastasis to the epididymis is seemingly an extremely rare finding in blastomycosis, as only two or three cases have been reported, and these in patients showing metastases in practically every other organ of the body. That our patient should have the disease for twelve years, and then suddenly develop a metastatic growth in probably the least often involved organ of the body, seems a most striking feature in this case.

That the organism can attack any single viscera or bony structure of the body we feel certain, in view of the cases we have mentioned and our own. No doubt a number of cases are never recognized. As in Brewer and Wood's [1] and Campbell's [2] cases, a diagnosis of tuberculous osteomyelitis was made, but was changed to blastomycosis when cultures were studied. Even microscopically, the true nature of the process can be misdiagnosed, as in our own case the pathologist reported the condition to be tuberculous until he was asked to search for the blastomycetes.

The most probable entrance for the organism is through the skin, although some cases, no doubt, begin in the throat and lungs. In our opinion, the mode of spread is by the blood stream, although blood cultures have failed in most instances. However, Stober [4] and Busse and Buschke [5] reported positive blastomycetic cultures from the blood, and, in a recent systemic case, we obtained a positive growth from blood cultures.

CONCLUSIONS

1. There are cases of local blastomycosis other than dermal.

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4. Stober, A. M.: Systemic Blastomycosis, Arch. Int. Med. **13**: 509 (April) 1914.
5. Busse and Buschke, quoted by Montgomery, F. H., and Ormsby, O. S.: Arch. Int. Med. **2**: 1 (Aug.) 1908.

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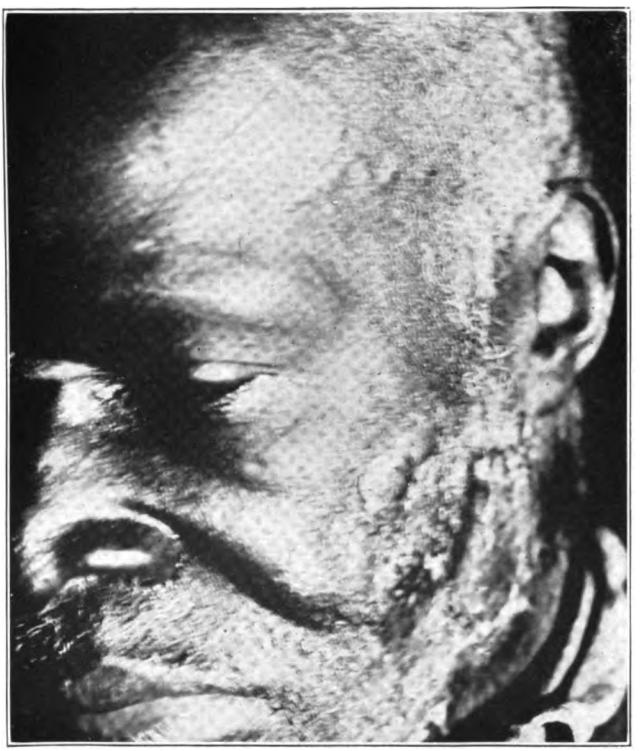

Fig. 1.—Lesion on left cheek.

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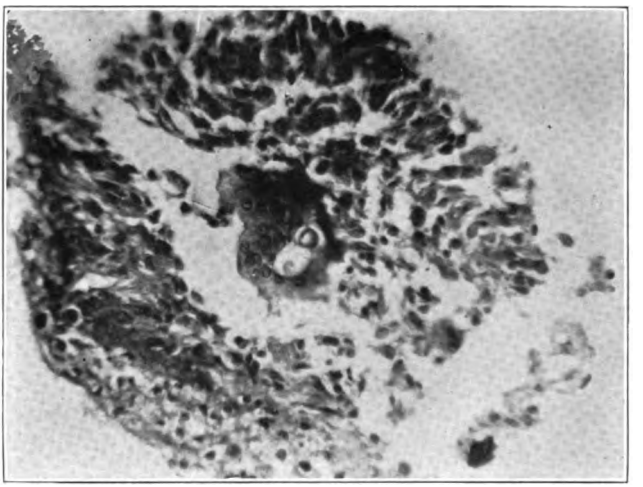

Fig. 2.—Organism in giant cell in tissue of epididymis.

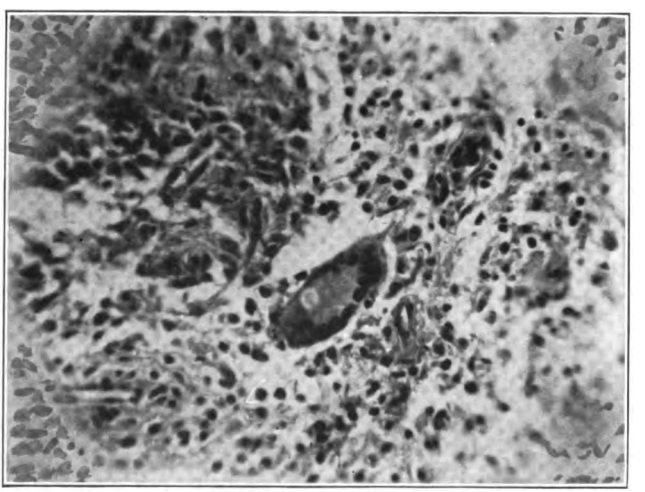

Fig. 3.—Organism in giant cell in tissue of epididymis.

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2. The organism may attack any organ or the bony framework.

3. The organism is probably spread through the blood stream.

ABSTRACT OF DISCUSSION

Dr. Francis E. Senear, Chicago: This paper is of great interest, reporting a case in which an isolated visceral lesion appeared some time after cutaneous lesions were under control. I do not think the profession looks on blastomycosis as a disease that is often complicated by visceral lesions. Many physicians do not attempt to understand any dermatoses, particularly the recently discovered types; and they regard blastomycosis as involving the skin alone. I have no doubt that many cases have escaped detection because the visceral picture was taken for something else. In 1913, I saw a patient with involvement of the face, hands and arms. At that time, there was a cough, with thick, bloody sputum; and chills, fever and night sweats. Under treatment, the skin lesions involuted in two months, and the patient felt like a new man. A month later he developed a cystitis of blastomycetic origin. Later, he had a prostatitis and, following this, an epididymitis of the left side, which subsided in about a month. In June, 1915, he developed a swelling in the left testicle. With this development, he became impotent. In October, 1915, the changes in the lung again became severe and the patient showed symptoms like those of tuberculosis. In a few months, he had a recurrence of the left epididymitis, and the testicle was involved at that time also. Within two months, an abscess was opened and drained. In May, 1916, he developed a nodule and abscess in the bursa of the left elbow. This disappeared under most intensive potassium iodid therapy, and radium applied locally. It was considered an abscess of blastomycetic origin, without the actual demonstration of the organism. One thing I would like to ask the essayists: In their case the left epididymis was involved as in our case, and I should like to know whether they noticed that the epididymitis was constant. I think it is generally understood that the involvement is more frequent on the left because of the anatomic structure, and it would be interesting to see whether it was true in all cases.

Dr. Louis E. Schmidt, Chicago: In one case which I had under observation, practically the same methods of examination were used for excluding all other conditions. It was originally a skin blastomycosis, treated for a long time, and finally a distinct involvement in the left epididymis took place. There were some blastomycosis lesions on the back and many on the scrotum. The epididymis was removed and the man made a satisfactory recovery. Most of the lesions

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on the scrotum healed. He disappeared from view for some time but reported later, when the opposite epididymis was involved, and this was also removed. After operating on this side, I referred him to the late Dr. Fred Harris, and I do not know the end-result.

Dr. J. M. King, Nashville, Tenn.: We have had several cases of blastomycosis and one was internally infected. In one elderly man, the neck and left side of the face were covered with lesions that extended onto his lip. Under treatment, most of the lesions healed. Later, they developed in the larynx, and the patient was operated on by a local man at Hopkinsville, Ky. He died a short time afterward. He had had a cough with heavy expectoration.

Dr. Earl D. Crutchfield, Galveston, Texas: We along the Gulf probably see more blastomycetic conditions than do men in other sections of the country. We have come to regard all of these lesions as points of origin for systemic invasion. In the last year, three cases have come under my observation which seem to be cases of systemic blastomycosis with local lesions, one on the hands, another on the elbow and one beginning on the toe. The one involving the hand showed roentgenographically lesions very similar to those of blastomycosis. The man subsequently developed malaise and had a temperature as high as 104 F.; but we were unable to demonstrate the presence of blastomyces in the blood stream. Clinically, however, we felt sure that this represented systemic invasion. The same thing occurred in a girl with a lesion on the elbow which we considered at first to be tuberculous because the roentgenogram showed bone involvement. After the blastomyces were demonstrated, the lesions in the skin healed very readily, only to break down later from an old infection in the bone. This condition, I think, in warm climates is liable to become a systemic disease, and any organ of the body may become involved.

Dr. Harold N. Cole, Cleveland: We have all seen cases of blastomycosis which did not seem to respond to any of the remedies recommended: arsphenamin, copper sulphate or any of those things. We have tried foreign proteins in some cases and the results are striking, accruing within twenty-four hours. I have seen the cutaneous picture change over night after an injection of 75,000,000 bacilli; in five days we give another dose of 125,000,000, and in another five days we give 150,000,000. A very severe reaction results, the local picture changes, and the condition seems to react more easily to other remedies after this treatment has been given. We have used the typhoid bacillus in this work.

Dr. Clement R. Marshall, Memphis, Tenn.: I am very glad to have heard these reports of cases, especially those with involvement of the epididymis, because in the literature it

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is very rare to find cases in which the epididymis was involved. One case was reported by Riley in 1903, in which both sides were involved, and another was reported by Hill, in which the right side was involved; so whether the left side is more liable to be affected or not, I cannot say. In the cases spoken of today, there was not the local involvement as in our case, but an invasion of every organ; so I think that our case is unique, in that it went along for years, and then suddenly involved the epididymis without other visceral metastases. Dr. Cole's treatment with foreign protein should be tried out thoroughly. The treatment with potassium iodid has not been very satisfactory in the systemic cases.

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EXPERIENCE WITH CHAULMOOGRA OIL DERIVATIVES IN TREATMENT OF LEPROSY *

HOWARD MORROW, M.D.
ERNEST L. WALKER, S.D.
AND
HIRAM E. MILLER, M.D.
SAN FRANCISCO

The recent encouraging reports [1] on the treatment of leprosy with the esters of chaulmoogra acid in the Hawaiian Islands induced us to give the leper patients at the San Francisco Hospital the benefits of this remedy. The extensive chemotherapeutic studies of Walker and Sweeney [2] at the Hooper Foundation of the University of California furthered our interest in the subject. Only by their active cooperation has this work been made possible. There have been from twenty to twenty-five patients with leprosy at the San Francisco Hospital for many years. When we began treating these cases, we did not anticipate the publication of our findings. The results, however, have been so at variance with our expectations and the impression obtained from the literature, that we feel some record should be made of them.

EARLY USE OF CHAULMOOGRA OIL

Chaulmoogra oil has long been recognized as the best remedy in the treatment of leprosy. Old Buddhist records in India of ten or more centuries ago refer to

* From the Department of Dermatology and the George Williams Hooper Foundation for Medical Research of the University of California Medical School.

1. Hollman, H. T., and Dean, A. L.: J. Cutan. Dis. **37**: 367 (June) 1919. McDonald, J. T., and Dean, A. L.: Pub. Health Rep. **35**: 1959 (Aug. 20) 1920. McDonald, J. T., and Dean, A. L.: The Constituents of Chaulmoogra Oil Effective in Leprosy, J. A. M. A. **76**: 1470 (May 28) 1921.
2. Walker, E. L., and Sweeney, M. A.: J. Infect. Dis. **26**: 238 (March) 1920.

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the improvement in infected persons after eating the raw chaulmoogra seeds. In modern times, Dyer,[3] Heiser,[4] Hopkins,[5] Connell[6] and Hollman[1] have reported improvement and even cures due to the administration of the whole oil by mouth over a long period of time. Marked gastric disturbances, and the length of time required to obtain results, made this mode of treatment unsatisfactory.

To overcome these disadvantages, the mixture of chaulmoogra oil with other substances to make it suitable for subcutaneous or intramuscular injection was attempted. The formula proposed by Mercado and Heiser,[7] consisting of chaulmoogra oil, 60 c.c.; camphorated oil, 60 c.c., and resorcin, 4 gm., has been used extensively. Heiser[8] reports the cure of twenty-eight patients by the use of this formula. Hopkins,[5] McCoy and Hollman,[9] Armellini,[10] Bercovitz,[11] Coghill,[12] Hall,[13] Cadbury,[14] Connell,[6] Hollman and Dean,[1] and others report cures or improvement in cases after the use of this and other combinations.

In 1916, Sir Leonard Rogers,[15] in India, reported the preparation of soluble salts of fractions of the fatty acids of chaulmoogra oil and their use intramuscularly and intravenously. He made three preparations of the chaulmoogric acids containing fractions of the lower, the medium and the higher melting points. The first preparation he called, arbitrarily, sodium gynocardate; the second, sodium hydnocarpate, as it contained a preponderance of hydnocarpic acid; and the third preparation, sodium chaulmoograte, as it contained

3. Dyer: New York M. News **87**: 199, 1905.
4. Heiser: Pub. Health Rep. **28**: 1855, 1913.
5. Hopkins, R.: New Orleans M. & S. J. **69**: 223 (Sept.) 1916.
6. Connell: J. Trop. Med. & Hyg. **22**: 37, 1919.
7. Mercado and Heiser: Pub. Health Rep. **28**: 1855, 1913.
8. Heiser, V. G.: New York M. J. **103**: 289 (Feb.) 1916.
9. McCoy and Hollman: U. S. Pub. Health Bull. 75, 1916, p. 3.
10. Armellini: Clinical Dermosifilopat d. r. University di Roma **35**: 109, 1917.
11. Bercovitz, Nathaniel: The Hypodermic Use of Chaulmoogra Oil in Leprosy, J. A. M. A. **68**: 1960 (June 30) 1917.
12. Coghill, H. S.: Ann. Trop. Med. **11**: 205 (Aug.) 1917.
13. Hall: Trop. Dis. Bull. **13**: 13, 1919.
14. Cadbury, W. W.: China M. J. **32**: 226 (May) 1918.
15. Rogers, Leonard: Lancet **1**: 288 (Feb. 5) 1916.

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more chaulmoogric acid than the other preparations. The latter preparation formed sodium salts too insoluble for use unless combined with other substances. After experimentation, he decided that the sodium hydnocarpate was more active than the sodium gynocardate. It was found [16] that sodium hydnocarpate could be prepared more readily and in larger quantities from hydnocarpus oil than from chaulmoogra oil. Rogers,[17] Cadbury,[14] Carthew,[18] Muir,[19] Peacock,[20] Connell,[6] Neve,[21] and others report the use of sodium gynocardate subcutaneously and intravenously with very good results. Rogers [22] and Muir [23] report even better results with the use of sodium hydnocarpate.

Rogers [24] tested the action of other oils with a large content of unsaturated fatty acids, namely, cod liver oil, linseed oil, Japanese sardine oil, and soya bean oil. He found the cod liver oil preparation, called by him sodium morrhuate, to be most effective. Advanced cases, treated with it, cleared entirely, and some patients who had ceased to improve with other preparations recovered completely when given sodium morrhuate intramuscularly or intravenously. Rogers concluded that the preparation of these different oils may be used to advantage in the treatment of leprosy. If a patient ceased to respond to one oil, the preparation of another oil should be substituted.

Harper [25] of India reports excellent results in the treatment of leprosy by intravenous injections of a mixture of chaulmoogra oil, sulphuric ether and iodin. Muir [26] also reports good results by this method of treatment; but he believes that better results are

16. Rogers, Leonard: India J. M. Res. **5**: 227, 1917.
17. Rogers, Leonard: Brit. M. J. **1**: 147 (Feb. 8) 1919.
18. Carthew, M.: India M. Gaz. **53**: 407 (Nov.) 1918.
19. Muir, E.: India M. Gaz. **53**: 209 (June) 1918.
20. Peacock, P. M. C.: India M. Gaz. **53**: 95 (March) 1918.
21. Neve: Report of a Conference on the Leper Problem in India, February, 1920, p. 41.
22. Rogers: Report of a Conference on the Leper Problem in India, p. 23.
23. Muir: Report of a Conference on the Leper Problem in India, p. 30.
24. Rogers, Leonard: Lancet **1**: 1178 (June 4) 1921.
25. Harper, in Muir's Handbook of Leprosy, Cuttack, 1921.
26. Muir: Handbook of Leprosy, Cuttack, 1921.

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obtained by the intramuscular or intravenous administration of a formula consisting of ethyl esters of the fatty acids of hydnocarpus wightiana, 1 c.c.; pure creosote, 1 c.c.; camphor, 1 gm., and olive oil, 2.5 c.c.

At the present time, Muir [26] is giving small doses of the ethyl esters of chaulmoogra acids intravenously at frequent intervals, with encouraging results.

The ethyl and other esters of chaulmoogric acids were first prepared by Power and his collaborators in 1904, during their extended investigation [27] of the chemistry of chaulmoogra oil at the Wellcome Chemical Research Laboratories in London from 1904 to 1907.

Notwithstanding the previous preparation of the esters by Power and the ancient use of chaulmoogra oil in leprosy, Ludwig Taub of Elberfeld, Germany, obtained patent rights in Germany in 1909 for the preparation of esters of chaulmoogra acids and their use in therapeutics. This patent right was assigned to a German chemical company, which put the ethyl esters on the market under the trade name of "antileprol." A little later, patent rights were also obtained in Great Britain and the United States. Following the war, and the confiscation of German patent rights, the alien property custodian sold the rights of this patent in the United States to the Winthrop Chemical Company of New York, which is preparing and distributing the ethyl esters of chaulmoogra acids under the trade name of "chaulmestrol."

In 1919, Hollman and Dean [1] reported the preparation and use by intramuscular injection of the ethyl esters of fractions of the fatty acids of chaulmoogra oil for the treatment of leprosy in Hawaii. These acids were separated into fractions by fractional crystallization, and these fractions converted into their

27. Power and Gornall: J. Chem. Soc. **85**: 851, 1904; Power and Lees: Ibid. **137**: 349, 1905. Power and Barrowcliff: Ibid., 884. Barrowcliff and Power: Ibid. **91**: 557, 1907. Power, F. B.: Am. J. Pharmacol. **87**: 493, 1915.

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ethyl esters. Four fractions in all were used. Groups of cases were treated with each fraction. It was decided that the therapeutic agent in chaulmoogra oil was distributed through all four fractions. This work was later carried on by McDonald and Dean, and is at present under the supervision of Dr. H. E. Hasseltine of the United States Public Health Service.

In 1919, Hollman and Dean [1] reported the treatment of twenty-six cases for less than two years, eight (30 per cent.) becoming bacteriologically negative in this time. In 1920, McDonald [1] reported the paroling of forty-eight cases; and in 1921,[1] ninety-four more cases were added, making a total of 150 cases.

These patients had been treated with weekly injections of the mixed ethyl esters of the acids of chaulmoogra oil, with 2 per cent. of iodin in chemical combination. This was supplemented by capsules containing the fatty acids of chaulmoogra oil with 2.5 per cent. of iodin chemically combined, given by mouth three times a day. In 1921, McDonald [1] reported series of cases treated without iodin and without chaulmoogra oil capsules. He concludes that "the oral administration is by no means necessary," and "the rôle of the iodin is at most a minor one."

This extended and varied empiric use of chaulmoogra oil and its derivatives in the therapeutics of leprosy was put on a scientific basis by the investigations of Walker and Sweeney,[2] at the Hooper Foundation for Medical Research of the University of California, in 1920. It was demonstrated experimentally that chaulmoogra oil contains substances having a high bactericidal activity in vitro. This bactericidal activity was found to reside in the fatty acids of the chaulmoogric series, and to be a function of the carbon ring structure which is peculiar to the chaulmoogric acids. The bactericidal action of these cyclic fatty acids was shown to be specific against the acid-fast groups of bacteria, and to be inactive toward all other bacteria.

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Furthermore, it was demonstrated that other unsaturated fatty acids, notwithstanding the therapeutic claims of Rogers and his colleagues, did not possess the specific bactericidal activity of the chaulmoogric acids. From the results of this experimental investigation, it was concluded that the empiric use of chaulmoogra oil and its derivatives in leprosy was justified, and that its therapeutic effect was due to the bactericidal action of the chaulmoogric acids on *Bacillus leprae*.

TREATMENT OF LEPERS AT THE SAN FRANCISCO HOSPITAL

In August, 1920, we began treatment of the lepers at the San Francisco Hospital, and they were under treatment up to March, 1922, when they were transferred to the national leprosarium at Carville, La.

Of a total of twenty-one cases, there were ten of the nodular type, six of the maculo-anesthetic type, and five of the mixed type. One had shown manifestations of the disease for two months, one for thirteen years, and the others for periods intermediate between these two extremes; the average duration of the disease was four and one-half years. Most of the cases were far advanced. The average period of isolation before beginning treatment was three years.

We employed chiefly the ethyl esters of the total fatty acids of chaulmoogra oil in our treatment. The injections were made intragluteally at weekly intervals, and the dosage was varied according to the weight of the patient and the amount of local and constitutional reaction after the preceding injection. The injections were not supplemented by chaulmoogra oil orally, or by the combination of iodin with the drug.

Laboratory investigations of the chemotherapeutics of chaulmoogra oil and its derivatives, which are being conducted by one of us simultaneously with the treatment of these patients, disclosed that two other esters, the butyl and propyl esters, produced much less local

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reaction and pain than the ethyl esters or any of a large series of derivatives prepared and tested. Therefore, these two new esters were substituted for the ethyl ester in the later treatment of our patients, and two lepers were treated exclusively with these esters. The clinical results confirmed the relative absence of local reaction obtained in the animal tests, and the therapeutic action appeared to be as good as that obtained with the ethyl esters.

SUMMARY OF CASES TREATED

Case	Name	Age, Years	Type of Disease	Duration	Severity	Duration Treatment	Average Dose, C.c.	Condition
1.	F. C.	22	Nodular	6 mo.	Moderate	3 mo.	3	Unimproved
2.	W. H.	27	Nodular	5½ yr.	Moderate	3 mo.	3	Unimproved
3.	L. C.	28	Mixed	5½ yr.	Moderate	2 mo.	3	Unimproved
4.	T.	41	Nodular	6 yr.	Advanced	10 mo.	3	Unimproved
5.	A. A.	34	Nodular	1 yr.	Moderate	3 mo.	3	Slight imp.
6.	L. Y.	27	Mac. anes.	3½ yr.	Moderate	5 mo.	3	Unimproved
7.	M.	24	Mixed	3 yr.	Moderate	8 mo.	3.5	Slight imp.
8.	G. H.	33	Nodular	3 yr.	Moderate	8 mo.	3	Unimproved
9.	D.	37	Nodular	10 yr.	Advanced	12 mo.	3	Worse
10.	S.	27	Nodular	5 yr.	Advanced	18 mo.	4	Worse
11.	W. K.	24	Mixed	2 yr.	Moderate	17 mo.	4	Much imp.
12.	Y. S.	45	Nodular	13 yr.	Advanced	9 mo.	3.5	Unimproved
13.	T. L.	36	Mixed	4½ yr.	Moderate	2½ mo.	3	Unimproved
14.	S. A.	53	Nodular	5 yr.	Advanced	13 mo.	3.5	Worse
15.	J. F.	15	Mixed	2 yr.+	Advanced	5 mo.	1	Died during treatment unimp.
16.	E. L. B.	71	Nodular	12 yr.	Moderate	11 mo.	4	Died, pneumonia unimproved
17.	F. W.	19	Mac. anes.	3 yr.	Moderate	14 mo.	3.5	Slight imp.
18.	G.	22	Mac. anes.	2 mo.	Mild	3 mo.	4	Absconded, unimp.
19.	J.	29	Mac. anes.	6 mo.	Mild	2½ mo.	3.5	Absconded, unimp.
20.	E.	47	Mac. anes.	6 mo.	Mild	8 mo.	4	Unimproved
21.	M.	45	Mac. anes.	2 yr.	Moderate	4 mo.	3.5	Much imp.

These twenty-one patients were under treatment for a period of from three to eighteen months, with an average of eight months. Of these patients, a boy, aged 15 years, with advanced leprosy, died of the disease; one man, aged 71, died of pneumonia-leprosy unimproved; three patients in advanced stages became definitely worse; nine showed no improvement; two patients with cases of moderate severity were markedly improved; three with cases of moderate severity were slightly improved, and two patients with the disease in an early stage absconded after three months' treatment.

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None of these patients became bacteriologically negative during treatment; but the nasal discharge in one case (Case 11) became negative after more than a year of treatment. The accompanying table, case reports and reproductions of photographs illustrate the results obtained.

TREATMENT AT KALIHI AND AT MOLOKAI

In consequence of the slow progress of most of these cases after treatment for fifteen months, it was decided to check up our results by a personal study of the treatment of lepers with the ethyl esters of chaulmoogric acids in the Hawaiian Islands. During December, 1921, one of us had the opportunity to see all the patients at Kalihi Hospital, Honolulu, and practically all the patients at the Molokai Leper Settlement.

There are 176 patients with lepra at Kalihi under the supervision of Dr. H. E. Hasseltine of the United States Public Health Service. These patients present all types of leprosy, from the earliest forms of maculo-anesthetic to advanced nodular. On account of all the very early cases of lepra in the Territory of Hawaii being segregated in Kalihi, that hospital is an ideal place for experimentation with the derivatives of chaulmoogra oil.

The various preparations used in treatment are made at the University of Hawaii under the supervision of Dr. A. L. Dean. At present, both at Kalihi and at Molokai, the preparations are used without the addition of iodin. The injections are given once a week, and until recently all injections were given into the buttock. Since the early part of January, 1922, Dr. Hasseltine has been giving a few patients small doses of the ethyl esters intravenously every few days. The latter method has the advantage of being painless.

Between 1918 and July, 1921, 150 patients were paroled from Kalihi; of this number, ten at least have

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died; a few have gone to other parts of the islands, and twenty (8 per cent.) have returned to Kalihi for further treatment as the result of recurrence of active symptoms of leprosy. It is likely that more of the paroled patients will show activity of the disease and will need further treatment.

The present system of paroling patients and giving them weekly injections of the ethyl esters for a further period of two years is a good one. It allows the patients to work, and with the continued medication there will be fewer recurrences, and many more patients are likely to be permanently cured.

During the six months previous to January, 1922, there were but six patients paroled. This small number of paroles indicates that the present authorities are using greater caution to prevent the discharge of arrested cases which are later liable to show exacerbations of leprosy. There are many patients with an advanced stage of leprosy at Kalihi, probably fifty of whom are incurable with our present method of treatment, and many of these should be sent to Molokai.

The settlement of Molokai contains 452 patients, and during 1921 more than 300 received treatment with the ethyl esters. As no patients with leprosy have been sent to Molokai since 1919, it is quite evident that very few early cases are to be seen there, and of the 300 receiving treatment, few, if any, show indications of an early parole. Dr. William Goodhue, the physician in charge of Molokai Settlement, is conscientious in giving the injections, and hopes to see many of the milder cases cured.

In conversation with Dr. Heiser, Dr. Trotter and many others who have had extensive experience in the treatment of leprosy, it seems to be the unanimous opinion that the present treatment with the esters is by far the best of any chaulmoogra oil treatments so far advanced. From bacteriologic studies and from clinical symptoms, it seems probable that the present system of

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Fig. 1 (Case 8).—No improvement after eight months' treatment.

Fig. 2 (Case 9).—Lesions more extensive after twelve months' treatment.

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Fig. 3 (Case 10).—Appearance of patient before treatment.

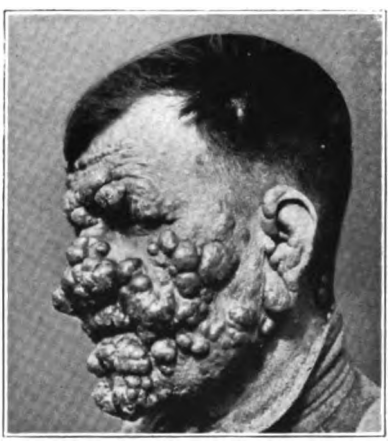

Fig. 4 (Case 10).—After eighteen months' treatment: lesions somewhat larger.

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Fig. 5 (Case 10).—Back of patient before treatment.

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Fig. 6 (Case 10).—After eighteen months' treatment: individual lesions smaller, but much more numerous.

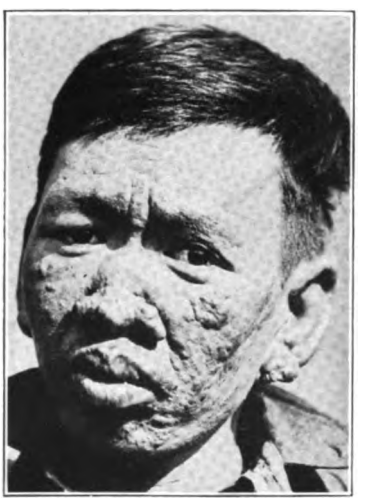

Fig. 7 (Case 11).—Before treatment.

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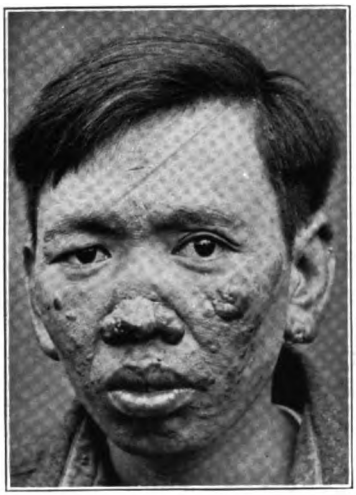

Fig. 8 (Case 11).—After seventeen months' treatment: most of nodules remaining are fibrous.

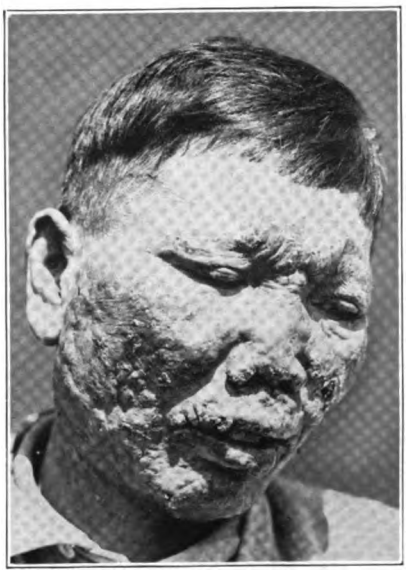

Fig. 9 (Case 12).—No improvement after nine months' treatment.

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Fig. 10 (Case 15).—Boy, aged 15, died of disease after five months' treatment.

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treatment will cure the early cases, especially in young subjects. The advanced cases certainly improve in time, and it is possible that many of these will be cured after years of treatment. Some of the advanced cases show little or no improvement after many months of treatment, and a very small percentage seem to do poorly under treatment.

In our cases of leprosy treated in San Francisco, the discouraging results are undoubtedly due to the age of many of the patients and the advanced stage of leprosy in most of them. In the few early cases we have treated, we are satisfied that the present remedy is of great value, and from statistics gathered we are also of the opinion that the injections must be kept up for at least three years in the milder cases and much longer in the advanced ones.

Isolation of all advanced cases of leprosy in one leprosarium in Louisiana is an excellent plan. Under government control and supervision these patients will receive much better treatment than when they were scattered in isolated county hospitals throughout the United States. We shall watch with much interest the results of treatment in this national leprosarium, and particularly the effect of further treatment in our individual cases.

REPORT OF CASES

Case 1.—F. C., a man, aged 22, born in China, who had leprosy of the nodular type, of six months' duration, was treated three months with an average dosage of 3 c.c. There were large nodules on the brow, and many small nodules on the cheeks, neck, chin and ears. There was marked tumefaction of the lobes of the ears. The trunk was normal except for a few pigmented macular areas on the back. There were a few similar areas on the forearms and arms, and many miliary semiconfluent nodular areas around the wrists. Tumefaction and pigmentation of the hands were well marked. There was no muscle atrophy. Compulsory treatment was discontinued after three months. The leprosy was unimproved.

Case 2.—W. H., a man, aged 27, born in Canton, China, had leprosy of the nodular type, of five and one-half years' duration. Treatment was given for three months with an average

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dosage of 3 c.c. There were alopecia and tumefaction of the brows; semiconfluent and confluent nodules on the nose, cheeks, chin and ears; diffuse, ill-defined, macular mottling over the shoulders, arms and forearms, and tumefaction of the backs of the hands. There was no muscle atrophy or sensory changes. Compulsory treatment was discontinued after three months. The leprosy was unimproved.

Case 3.—L. C., a man, aged 28, born in China, had leprosy of the mixed type of five and one-half years' duration. The symptoms began six months before entrance. The patient was under treatment for a period of two months, with an average dosage of 3 c.c. There was diffuse but not marked thickening of the forehead, brows, nose and cheeks. The ears were enlarged, especially in the lobes. There was a geographic macular eruption on the neck; a coin-sized, well defined macular eruption on the trunk, anterior and posterior; diffuse macular areas on the arms and forearms; multiple, miliary nodules on the wrists, and tumefaction of the hands; a diffuse, leprous thickening of the right palm. The ulnar nerves were moderately enlarged; there was thenar and hypothenar atrophy, especially of the right hand. There were confluent nodules over the right elbow tip simulating xanthoma. There were geographic areas on each thigh, and nodules on the right buttocks. The patient took treatment under compulsion, and discontinued it after two months. No improvement was noted.

Case 4.—T., a man, aged 41, born in Greece, had leprosy of the nodular type, of five years' duration. The patient was under treatment for a period of ten months. The average dosage was 3 c.c. each week. There was worm eaten alopecia of the scalp of six years' duration, simulating syphilis. The eyes were normal; the trunk, thighs and arms clear; the cheeks shiny and red, with many telangiectases and comedones. Small nodules and stains were scattered over the face. The brows and lashes were gone. The ears were enlarged and wrinkled. The hands and forearms were nodular. There was passive congestion in the hands; the normal lines of the palms were accentuated. On the legs, around the knees, were deep, dark scars. There were ulcers on each calf. There were nodules and hyperkeratosis of the soles. The condition in March, 1922, was more advanced.

Case 5.—A. A., a man, aged 34, born in India, had leprosy of the nodular type, of one year's duration. Treatment was given for three months. The average dosage was 3 c.c. There was alopecia of the brows. There was thickening with scattered small nodules over the face, cheeks and chin. The nose was broadened and flattened. The trunk was practically clear. There was marked tumefaction of the hands and feet, and considerable ulceration and secondary infection on the feet. In March, 1922, all the areas were slightly improved. The patient's general health was improved.

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CASE 6.—L. Y., a man, aged 27, a Chinese, had leprosy of the maculo-anesthetic type, of three and one-half years' duration The patient was under treatment for a period of five months. The average dosage was 3 c.c. The brows, nose and ears were normal. There were confluent and diffuse macules on the face and neck. A few chicken-egg sized anesthetic rings were noted on the chest. The hands were distinctly claw-shaped, and all the muscles were atrophied. The arms and thighs were covered with diffuse, anesthetic, geographic areas. Compulsory treatment was discontinued after five months, with the leprosy unimproved.

CASE 7.—M., a man, aged 24, born in Hawaii, with leprosy of the mixed type, of three years' duration, was given treatment eight months. The average dosage was 3.5 c.c. There were about a dozen discrete and comparatively flat nodules on the forehead, cheeks and chin, confluent on the right cheek. There was faint tumefaction of the ears. There was a diffuse, confluent and semiconfluent macular eruption on the trunk and thighs. Tumefaction was noted on the backs of both hands. A few small nodules were located on the wrists and forearms. There was no disturbed sensation or muscular atrophy. Compulsory treatment was discontinued after eight months. The nodules on the face were smaller. The macular areas on the body were less distinct.

CASE 8.—G. H., a man, aged 33, a Japanese, with leprosy of the nodular type, of three years' duration, received treatment for eight months. The average dosage was 3 c.c. There were about two dozen small, flat nodules on the cheeks, lips and chin. The ears were large, nodular and pendulous. There was a faint, miliary, papular rash over the trunk and thighs. There was tumefaction over the backs of the hands. The palms were dry, the normal lines increased. After eight months' treatment, the patient complained of general malaise and severe pains all over the body a few hours after each injection. The injections were discontinued. The leprosy was unimproved.

CASE 9.—D., a man, aged 37, an American, with leprosy of the nodular type, of ten years' duration, was given treatment for twelve months. The average dosage was 3 c.c. There were discrete and confluent nodules over the entire face. The nose and ears were ulcerated. There was total alopecia of the brows. The patient was blind in both eyes. There was a diffuse, lichenoid, leprous dermatitis from the scapulae to the buttocks. A similar condition existed on the buttocks, with scattered nodules throughout. There were crenated skin and lichenoid dermatitis on the thighs. A diffuse and marked tumefaction was present on the backs of the hands and fingers. In March, 1922, the condition of the lesions was more advanced.

CASE 10.—S., a man, aged 27, a Portuguese, with leprosy of the nodular type, of five years' duration, was treated

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eighteen months. The average dosage was 4 c.c. Nodules from the size of a pea to that of a pigeon's egg covered the face. Some lesions were almost pendulous. A few ill-defined nodules were on the tongue and hard palate. There were semipendulous and semiconfluent nodules over the hands and forearms, small nodules over the palms, and scattered pea to lima bean sized semipendulous nodules over the trunk. There was no muscle atrophy. In March, 1922, the lesions were somewhat larger and more extensive.

Case 11.—W. K., a man, aged 24, with leprosy of the mixed type, of two years' duration, was treated seventeen months. The average dosage was 4 c.c. Pea-sized nodules were scattered over the forehead, cheeks, nose and ears. Some areas were soft, and some fibrous. A few small nodules were scattered on the forearms. There were geographic, cyanotic macules on the trunk, a chronic lichenoid leprid of the thighs, and solid edema of the backs of the hands. The ulnar nerves were enlarged. There was contracture of the little and ring fingers. The nasal secretions contained many lepra bacilli. These disappeared after one year's treatment. In March, 1922, many nodules had disappeared, leaving pigmentation. The remaining nodules were fibrous and apparently inactive.

Case 12.—Y. S., a man, aged 45 years, a Chinese, with leprosy of the nodular type, of thirteen years' duration, was treated nine months. The average dosage was 3.5 c.c. There were confluent, pea-sized, subcutaneous nodules over the entire face. The nose was flattened and partially destroyed. There were ulcerations on the nose, lips and cheeks. There was almost complete alopecia of the brows. The skin of the trunk was dry and scaly, with hyperpigmentation over the lower back. There was edema of the backs of the hands and the feet. Compulsory treatment was discontinued after nine months. The leprosy was unimproved.

Case 13.—T. L., a man, aged 36, a Chinese, with leprosy of the mixed type, of four and one-half years' duration, was treated two and one-half months. The average dosage was 3 c.c. A few faint, indistinct nodules were seen on the upper lids. There was considerable atrophy of the skin of the face, apparently the result of the absorption of leprous lesions. Small cutaneous and subcutaneous nodules were grouped on both forearms. There were pigmentation and crenated skin on the backs of the hands, and contracture and atrophy of all the fingers on the right hand, associated with marked anesthesia. There was very little contracture or atrophy of the left hand. The condition, after two and one-half months of compulsory treatment, was unimproved.

Case 14.—S. A., a man, aged 53, an American, who had contracted the nodular type of the disease in the Philippines, five years before, was given treatment thirteen months. The average dosage was 3.5 c.c. The forehead was wrinkled and

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hypertrophied. There were about two dozen small nodules on the cheeks, chin and lips. The left eye had been removed two and one-half years before because of corneal involvement. The entire right eye was blurred; the pupil was irregular from synechiae. The entire body had a faint, wrinkled, pigmented, scaly appearance. The condition of the hands was similar, but more advanced. Very little, if any, atrophy was present. In March, 1922, the patient was totally blind. The nodules on the face were larger. The general health of the patient was very poor.

CASE 15.—J. F., a boy, aged 15 years, a German, born in Honolulu, with leprosy of the mixed type, of probably two years' duration, was treated five months. The average dosage was 1 c.c. The patient weighed 50 pounds (22.7 kg.). There was total alopecia of the brows. The nose, ears, lips, cheeks and chin had been partially destroyed by ulcerating nodules. There were dry, faint, mottled and macular areas over the trunk and the extremities. There were tumefaction of the backs of the hands and contracture of the little fingers on both hands. The patient's general condition was much improved after two months' treatment; it became gradually worse, however, and he died of the disease after five months' treatment.

CASE 16.—E. L. B., a man, aged 71 years, an American with leprosy of the nodular type, of twelve years' duration, was treated eleven months. The average dosage was 4 c.c. The patient was blind in both eyes. The skin on the face was atrophic from absorption of nodules. There was a diffuse, leprous, lichenoid dermatitis over the back, abdomen and the sides of the body; a faint, diffuse, gyrate mottling over the chest and the thighs and crenated skin on the forearms. The backs of the hands were dry, wrinkled, crenated and bluish. There was no muscle atrophy. The patient died of pneumonia after eleven months of treatment, with the leprosy unimproved.

CASE 17.—F. W., a man, aged 19, a Chinese, with leprosy of the maculo-anesthetic type, of three years' duration, was treated fourteen months. The average dosage was 3.5 c.c. There was elephantiasis of the upper and the lower lip. On the face, neck and upper part of the back there were faint, ill-defined, macular areas. The toes and fingers were markedly contracted with considerable atrophy. Both ulnar nerves were definitely enlarged and nodular. The hands and areas on the forearms were anesthetic. In March, 1922, the macular areas were disappearing; otherwise the condition was unchanged.

CASE 18.—G., a man, aged 22, born in the Philippines, with lepropsy of the nerve type, of two months' duration, was treated for three months. The average dosage was 4 c.c. each week. The right ulnar nerve was about the size of a little finger. The right little finger was contracted. The side of

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the wrist and palm innervated by the ulnar nerve showed a brownish pigmentation with accentuation of the normal lines. This entire area was anesthetic. The patient absconded after three months' treatment with the leprosy unimproved.

CASE 19.—J., a man, aged 29, born in the Philippines, with leprosy of the nerve type, of six months' duration, was treated two and one-half months. The average dosage was 3.5 c.c. each week. Hyperpigmented and depigmented areas were scattered over the body. Half a dozen dollar sized rings were scattered over the buttocks and the back. There was slight tumefaction of the backs of the hands, with an accentuation of the normal markings on the palms. A similar condition prevailed on the soles. There were small ulcers on the great toes. The patient absconded after three and one-half months' treatment, with the leprosy unimproved.

CASE 20.—E., a man, aged 47, an American, with leprosy of the maculo-anesthetic type, had spent some time in Brazil sixteen years before. The duration of the symptoms was six months; the duration of treatment, eight months. The average dosage was 4 c.c. A palm-sized fawn-colored, anesthetic macular area was situated just above the left internal malleolus. After seven months' treatment, erythematous macular anesthetic areas appeared on the upper lip and the right cheek. A few months after beginning treatment, the area on the leg was barely visible; at present, however, it is about the same as at the time when the patient was first seen. After eight months of treatment, he complained of general malaise with pains in the muscles and joints that were so severe that they prevented him from working. Treatment was discontinued for two months.

CASE 21.—M., a man, aged 45, an Englishman, probably contracted the disease in South Africa. The duration of symptoms was two years. The disease was of the maculo-anesthetic type. He was under treatment for a period of four months. The average dosage was 3.5 c.c. Erythematous, macular areas were situated on the left chin, left temple and left ear. The left posterior lumbar region was covered with an extensive, erythematous, macular eruption. There was a small macular area on the right anterior wrist. The macular areas were all anesthetic to pin pricks, heat and cold. After one month's treatment, the areas on the back and wrist became pigmented, and sensation began to return. At present, after four months' treatment, the pigmented areas are fading, and the skin is returning to its normal state. The areas on the face are involuting more slowly. There is general malaise, with pains in the joints and muscles of such severity that the patient is confined to bed for three or four days after each injection. Treatments were discontinued for three or four weeks. The patient was given sodium cacodylate injections during this rest period.

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ABSTRACT OF DISCUSSION

Dr. William T. Corlett, Cleveland: The paper is fair and comprehensive. Its conclusions, however, may be a little too optimistic; but optimism, next to the actual curative agent, is the stimulus that the leper needs. Since the parole system was adopted in the Hawaiian Islands in 1918 or 1919, the leper himself has received a new lease of life. That the community is more endangered is another question. He has felt that it is possible for him to become rid of the malady, which is a valuable curative asset in any disease. As to the treatment of leprosy with the ethyl esters: So far as I can ascertain, they bring out no beneficial properties not possessed by the old chaulmoogra oil itself—when the patient can take chaulmoogra oil. But the crude oil is often irritating to the stomach, and many patients cannot take it. In such instances the intramuscular, or better, the intravenous, administration of the ethyl esters is a decided advantage. The separation of the ethyl esters made available in 1904, or soon after, must be, therefore, considered a step in advance. A few weeks ago when I left Honolulu, Dr. Hasseltine, the marine and public health officer, was giving, when possible, the ethyl esters intravenously, and this to my mind will prove to be the future treatment for leprosy. The use of the ethyl esters intramuscularly, into the buttocks, is painful, much more so than the same method of giving mercury. Even when patients are willing to submit to it, there are disadvantages. I recall two cases in which extensive abscesses followed this procedure, while the introduction into the veins is painless. If the ethyl esters can be rendered sufficiently innocuous to be introduced safely into the veins, it would be the best treatment of leprosy so far as relates to the ethyl esters or the newer derivatives of chaulmoogra oil.

Dr. R. M. Wilson, Korea: I have 800 patients with leprosy under my care. I have trained our lepers to do their medical work and use the microscope, as well as other laboratory work, and I am enthusiastic about chaulmoogra oil. I believe that chaulmoogra oil is as good as the ethyl esters because it contains many things the ethyl esters do not. We have been using chaulmoogra oil, 1 per cent., and for six months we have been using the ethyl esters, but the ethyl esters have not affected the old cases treated by chaulmoogra oil. Either the ethyl esters or chaulmoogra oil in a new case will show quite marked results in six months' time. I think that in the cases shown this morning we could hardly hope to see much improvement, because the cases are so advanced. The great hope is in the younger cases, particularly the children, who respond more readily. We find in some cases that improvement takes place under hypodermic injections before the internal treatment is effective. In our institution we have the industrial work pretty well estab-

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lished; these patients do brick and tile work, and they prefer to take the capsules internally and that seems to hold them in check. Many cases are not entirely healed, but they are held in check. I have 300 patients on the ethyl esters in Peking and 200 on chaulmoogra oil, and hope to report in a year's time which gives the best results. These lepers come in literally crawling in the dust, feeling that they are dead dogs, and then when they come to realize that we can do something for them they are the happiest group you can find. I am very enthusiastic about the ethyl esters, and believe there is no doubt that we can get splendid results in the early cases.

Dr. I. L. McGlasson, San Antonio, Texas: In San Antonio we have about thirty cases of leprosy, not that number under treatment, but that is about the number we have proved. This paper is a wonderful article on the class they have attempted to treat, but I believe that the problem in leprosy is the same as in tuberculosis and cancer—there are cases we cannot touch. I think that it is unfair to draw conclusions from the old and hopeless cases. It is the early case in which we can do the most good. I am going to advance another opinion, and that is that many cases are not recognized. They occur not in the poorer class but in the better classes, and yet they are lepers. The class in which we get the best results, in my experience, consists of early cases, when the patients are in fine shape physically and mentally. I think the point is well taken by Dr. Corlett as to the time when they will return. A certain percentage will recur, which indicates that we have stopped treatment early. We have no means of knowing when they can be discharged as cured and when they can stop treatment. Whether this is the best treatment or not, we are on the right track to get a treatment which can offer something if we get the cases in time. My experience is that in the + and ++ Wassermann reactions that cannot be substantiated clinically, if one will investigate the nose and the skin, one will probably find some evidence of leprosy. Let us keep an open mind on this. The cases in California were far advanced, and it would take a long time before they could be influenced by the ethyl esters or chaulmoogra oil; but in the early cases I am sure that a great deal can be accomplished, and many patients cured.

Dr. Ernest D. Chipman, San Francisco: The cases reported were old, but I know from personal conversation with Dr. Morrow that they have taken the cases as they found them, and that they thoroughly believe in the efficacy of the treatment in early cases. Dr. Corlett, and I think Dr. Wilson also, expressed the view that a very important feature in leprosy is the moral effect produced by the introduction of a treatment that gives the patients some hope. I

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have had an opportunity of visiting the hospitals in Honolulu twice during the last few years, and have been much impressed with the apparent happiness with which patients faced their hospitalization. Whereas in former times they made every effort to conceal the disease, they now come voluntarily for treatment.

Dr. Floyd Stewart, St. Louis: I had the pleasure of treating many of these patients with Dr. Isadore Dyer of New Orleans. Dr. Dyer first began using potassium chlorate, sodium salicylate and strychnin. He reported a case as a probable cure because all the lesions cleared up. The patient was dismissed from the Charity Hospital outclinic, and was not taken to the leper colony. At that time it was purely voluntary; there were no laws to transport these people, and this patient, a negro, returned to work; but in about eighteen months he came back for further treatment. At that time Dr. Dyer took up another treatment, called the "antivenin" treatment. He purchased this serum from the Calmette Laboratory at Lille, France, and it gave remarkably good results at first. Following this case we had several that showed improvement for a certain length of time, and then retrogressed. Dr. Dyer discussed the use of the antivenin serum, not on account of the cost, which he had defrayed himself, but because of the poor final results. Then he took up this new treatment with chaulmoogra oil. He was rather enthusiastic about the results he was obtaining. I hope that Dr. Morrow's results are encouraging enough for him to persist in treating these cases, and that he will succeed in curing the mild cases at least, for it is quite evident that when physicians and patients are enthusiastic about a remedy, better results will be obtained.

Dr. Edward A. Oliver, Chicago: We have had about seven of these cases under treatment in the Cook County Hospital and have been very enthusiastic about the ethyl esters. Six were of the nodular type and one of the maculo-anesthetic type. We first started on chaulmoogra oil, and then when we received the ethyl esters we used them. There was no patient who did not improve, but they were only moderately advanced cases. One patient was a Serbian, and he improved very rapidly, all of the lesions disappearing. One man we have paroled now. Every one of these patients improved mentally, physically and in every other way under the ethyl ester treatment.

Dr. Hiram E. Miller, San Francisco: In presenting this paper we had only hoped to moderate the impression that advanced cases of leprosy were being readily cured by the injection of ethyl esters over a comparatively short length of time. However, I would like to emphasize the fact that we feel that early cases in young persons may be cured with the present methods of treatment.

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LEUKOPLAKIA BUCCALIS

H. H. HAZEN, M.D.

AND

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This disease was first described by Sigmund, and a few years later by Bazin, as lingual psoriasis. Schwimmer,[1] in 1877, first described leukoplakia under its present name, and definitely separated it from psoriasis. Probably the best descriptions of the condition are found in Butlin's [2] "Diseases of the Tongue," and in Fordyce's [3] excellent article. In 1915, Levy [4] reviewed the subject and his article contains an excellent bibliography up to that date. Since 1915, there have appeared in the world's literature only three references to this disease. They are by C. C. Crunston and by E. C. G. Little, and are scarcely more than case reports. The only comprehensive article is by G. Raillet,[5] in which he analyzes seventy-seven cases of leukoplakia and draws some general conclusions, which may be summarized by saying that he believes that some cases may be of syphilitic origin, but that syphilis is not essential to producing this disease. Bloodgood [6] in his article on cancer of the tongue gives a review of his experience with leukoplakia.

SYMPTOMATOLOGY

Leukoplakia is not confined to the mouth alone. It is comparatively common on the vulva, and occasionally occurs in the vagina, uterus, urethra, bladder and pelvis of the kidney.

1. Schwimmer: Arch. f. Dermat. u. Syph., 1877, p. 511.
2. Butlin, H. T.: Diseases of the Tongue, London, Cassell & Co., Ltd., 1900.
3. Fordyce: Some Affection of the Oral and Nasal Cavities That Are Related to Skin Diseases, New York M. J., March 6, 1906, p. 465.
4. Levy: Tr. Am. Laryngol. Ass., 1915, p. 84.
5. Raillet: Bull. et mem. Soc. med. d. hôp. de Paris **43**: 325 (April 4) 1919.
6. Bloodgood, J. C.: Cancer of the Tongue: A Preventable Disease, J. A. M. A. **77**: 1381 (Oct. 29) 1921.

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The first evidence is a bluish-white or, more rarely, a bluish-red patch on the mucosa, which is often sensitive to either chemical or thermal irritation. We have seen such a patch develop in one week's time as the result of irritation from a rough tooth. At this stage, the condition frequently escapes notice. When first seen by the physician, the patient usually presents a pearly or milky white, slightly indurated patch on the mucous membrane of the tongue or the buccal surface of the cheeks, or, more rarely, of the gums. Patches are sometimes seen on the lips, and here are often the result of chronic syphilitic mucous patches. The area involved may be but a centimeter in diameter, or may involve the entire buccal mucosa and tongue, and even extend into the larynx. The diseased area may be very thin, or it may be so thick and indurated that it is difficult to tell whether or not malignant degeneration has occurred. Cracking, fissuring and ulceration are late stages. Cracking and fissuring in slight lesions of the tongue are frequently the result of syphilis, and any extensive ulceration usually means cancer.

REPORT OF CASES

CASE 1.—G. R., aged 24, a moderate smoker, whose teeth had many rough edges and cavities, and whose reaction was negative for syphilis, clinically and serologically, was cured by careful dentistry. He acquired syphilis two years later. This was a mild buccal case.

CASE 2.—Major M., aged 35, a heavy smoker, with very bad teeth, whose test for syphilis was negative, clinically and serologically, presented an advanced case of leukoplakia of the tongue. The patient refused to stop smoking; and there was no improvement after the teeth were cared for. The patient was lost sight of.

CASE 3.—Mrs. G. F., aged 60, whose teeth were bad, and in whom tests for syphilis were negative, clinically and serologically, presented severe leukoplakia of the tongue with well developed cancer. She died in spite of radical surgical intervention.

CASE 4.—B. D., man, aged 40, a heavy smoker, and with bad teeth, whose Wassermann reaction was positive, was unaffected by antisyphilitic treatment although it was extensive and severe. The teeth were not attended to and the patient continued to smoke. He was lost sight of.

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CASE 5.—Colonel W., aged 52, who smoked three cigars a day, and whose teeth were rough, gave a negative reaction to clinical and serologic tests for syphilis. The condition cleared up under simple dental care. This patient has been well more than a year, and still smokes as before.

CASE 6.—Mr. G., aged 55, who chewed tobacco and whose teeth were very bad, gave a negative reaction to clinical and serologic tests for syphilis. This was an extensive case. According to the history, it started in the cheek in which the tobacco was habitually held. The teeth were repaired, tobacco stopped, and roentgen-ray treatment given, but no improvement was noted. The patient was lost sight of.

CASE 7.—Miss K., aged 60, who did not smoke or use tobacco and in whom rough teeth were present, had a moderately severe buccal leukoplakia. Syphilis was excluded. The patient was permanently cured by smoothing off the teeth and using the cautery locally.

CASE 8.—Mr. S., a moderate pipe smoker, whose teeth were very bad, and in whom syphilis was excluded clinically and serologically, presented a moderately severe case, which was cured by cleaning up the teeth and using the cautery locally. This patient is still smoking.

CASE 9.—B. F., man, pharmacist, aged 45, with a negative history of syphilis, whose Wassermann reaction was ± with cholesterin, negative with plain antigen, and examination negative for syphilis, was a heavy smoker. He was referred for an ulcer behind the last lower left molar tooth, which proved to be a well marked cancer. He presented a patch of verrucose leukoplakia on the buccal mucosa just inside of the angles of the mouth, about 1 cm. in diameter, and similar lesions about 3 cm. in diameter on the buccal mucosa opposite the posterior teeth, which had extended to the gums. One of these had degenerated as noted. The patient stated that the white colored mucous membrane had started on the cheeks just opposite bad teeth. The upper teeth were drawn a week before and were said to have been worse than the lower, which were certainly rough and badly diseased. The patches just inside the lips were opposite the natural position of the cigar end.

CASE 10.—A man, aged 65, whose tests were negative clinically for syphilis, and who did not smoke, had a patch of early leukoplakia opposite a rough tooth. He is still under observation. This condition was discovered in routine examination. Parenthetically, we would note that many such cases have doubtless been overlooked, by ourselves as well as others.

ETIOLOGY

1. *Syphilis.*—This condition was positively diagnosed but once was positively excluded, so far as possible, in seven was doubtful in one and not absolutely excluded

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in one. Seventy per cent. at least, therefore, could probably be attributed to nonsyphilitic causes. On the other hand, in twelve cases reported in recent years in the American literature, four cases were positive for syphilis, six were negative, and in two no note is made regarding syphilis; while Bloodgood reports positive Wassermann reactions in 27 per cent. of 33 cases.

2. *Tobacco.*—Seven of our patients used tobacco in some form, three to excess, and two of these had cancer when first seen. Two of the patients were cured without giving up tobacco. Three did not use tobacco. In the twelve cases previously reviewed, seven patients used tobacco and one did not, and in four cases there were no notes on this subject. Bloodgood states that all his cases give a definite history of excessive use of tobacco.

3. *Teeth.*—In all ten of our cases, a definite note of rough or diseased teeth is recorded. Bloodgood records bad teeth in all but one case of leukoplakia. On the other hand, in the twelve cases found in the literature, the condition of the teeth is noted in only one case, in which rough and diseased teeth were found. It is interesting to note in this connection that in our private series of the four cases that were mild enough to be cured, two cleared up by the simple procedure of caring for the teeth properly, and the other two by this treatment plus the cautery. Out of a total of fifty-five cases, there were bad teeth in forty-three, and no notes regarding dental trouble in eleven. In the same number of cases, syphilis was definitely excluded in thirty-five, and was very doubtful in six. Forty of the patients used tobacco in some form, and four who had never used tobacco had a well marked leukoplakia. Two of our patients were cured without discontinuing the use of tobacco.

As a result of these observations, the following deductions seem logical: 1. Syphilis represents an accidental rather than a causative factor in this disease. 2. The use of tobacco is not necessarily a factor.

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3. Rough teeth, by causing mechanical irritation, inaugurate the disease in the vast majority of cases.

We would call attention to the fact that, etiologically, leukoplakia is analogous to keratosis of the skin, in that the former is a defense reaction against mechanical irritation in the mouth, the latter a defense reaction against the actinic rays or mechanical irritation, or both, on the skin. Each develops as a result of functional overactivity.

ETIOLOGIC FACTORS AND NUMBER OF CASES

	Positive	Negative	Doubtful, or Not Noted
Syphilis	14	35	6
Tobacco	40	4	11
Teeth	43	1	11

PATHOLOGY

Most observers, ourselves included, agree with Fordyce that the earliest change is an inflammatory process in the papillary region, with secondary hyperkeratosis. Once the disease is developed, there is found marked hyperkeratosis, acanthosis with thickening and prolongation of the rete pegs, so that the papillae may become obliterated, and an inflammatory infiltration of the corium with small round cells. There may be distinct fibrosis of the deeper layers in more advanced cases. Here again there is an analogy with senile peratosis, the pathologic picture being very similar.

CLINICAL COURSE

These cases are extremely rebellious. They tend to remain stationary or gradually to progress over a period of months or years. They are distinctly precancerous. Many cases have already developed cancer when first seen—two of our ten—and those that fail to clear up under treatment should be carefully observed periodically and radical procedures instituted the minute ulceration or fissuring with increased induration indicates the development of cancer. In the tendency to carcinomatous degeneration, we have a third resemblance to the keratosis on the skin.

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TREATMENT

Whether syphilis is present or not in a case of leukoplakia, antisyphilitic treatment is of no avail, and need not be considered in the treatment. Some of the earlier cases will clear up if the source of irritation is removed. We believe this will nearly always be found in the teeth. However, as tobacco is undoubtedly a very important factor, its use should be interdicted. These two steps should always be employed, because, whether they are the cause of the leukoplakia or not, cancerous degeneration may thus be warded off. If the cases are very extensive and severe, no treatment is likely to avail, even radium, according to MacKee, being useless. A majority of cases that are not already carcinomatous will fall into the following group. They will not disappear with removal of the cause alone, but can be cured by appropriate destructive treatment. In our hands, the roentgen ray has been of no use. We have had no experience with radium, but its users are enthusiastic. MacKee advocates an erythema dose with an unfiltered plaque, believing that the beta ray is the most efficient. Others advocate the use of gamma rays only. In our hands, the best agent has been the cautery. This is used at red heat, with local anesthetic. With a little experience, one can learn to burn deep enough to destroy all leukoplakia, and yet leave a functioning membrane.

ABSTRACT OF DISCUSSION

Dr. Francis E. Senear, Chicago: It has been my belief that not all cases of leukoplakia are of syphilitic origin. I believe this opinion is rather generally accepted. I have been in the habit of avoiding treatment in those cases in which the leukoplakia has not been severe and in which there has been no evidence of degeneration of the mucous membrane, disliking to replace the mucous membrane with scar tissue. I am glad to hear Dr. Eichenlaub's results with the cautery. I have used radium and the roentgen ray without excessively satisfactory results, and have become an advocate of the use of the actual cautery in many dermatologic conditions during the last few years. It seems to me that the cautery might be an admirable thing to use in these

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cases. It does not set up any radiodermatitis, which would be as dangerous as the original leukoplakia.

Dr. William H. Guy, Pittsburgh: This paper is interesting because it crystallizes opinion as it exists today as to the cause of the leukoplakia. We should realize that we are dealing with a lesion that is due to irritation, and that mouth hygiene is of prime importance from the standpoint of prophylaxis. Therapeutic suggestions interest me most, because I advocate the use of radium, and being a pupil of MacKee, naturally my technic is his. We use one-half strength flat applicators unscreened, covered with rubber to remove secondary rays from the metallic edges, leaving them in place long enough to get a reaction. This means varying lengths of time, from ten to twenty minutes, never using the one-half strength applicator for longer than half an hour. In this way we get a fairly sharp localized reaction. The treatments are never repeated until the reaction following the first application has entirely subsided. The results are favorable in a fair number of cases. I do not think that any one method of attack in all cases will be successful. We occasionally find cases in which more than ordinary treatment is advisable. In deep, infiltrated lesions, a filtered application is definitely indicated. In such cases if only a plaque is available, one should use complete filtration and leave it in place for from eight to ten hours. If tubes are used, a corresponding dosage may be given. In superficial lesions the beta ray is used because depth penetration is not only not necessary, but actually undesirable. Radium, of course, is not the only treatment, and, perhaps, not always the method of choice; but it certainly is of definite service in the majority of cases.

Dr. J. M. King, Nashville, Tenn.: I wish to endorse the method Dr. Guy mentioned. I use the flat plaque with very good results. I am under the impression that the cautery should be used in the deep or thickened patches. Radium could be used, but I would prefer the radium in the cases Dr. Guy mentioned.

Dr. William T. Corlett, Cleveland: There is at least one good feature of a long medical career because it enables one to see fashions in medicine come and go. I treated quite a number of cases of leukoplakia during the eighties and nineties of the last century with electrolysis, with very good results. Since then, however, other methods have come into vogue, and I have used in turn the roentgen ray and radium, so that I believe I am in a position to judge without prejudice the merits of at least three methods mentioned for this disease. I might say, in addition, that the subject of syphilis, in my experience, might be excluded in the etiology of the disease. First, then, in the treatment by electrolysis, as first advised by Dr. Hardaway a number of years ago and used by him and other dermatologists for hypertrichosis and

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various other cutaneous conditions, including cases of leukoplakia, the results in my experience were better than they have been with either the roentgen ray or with radium. I wish to emphasize the point made by Dr. Senear in regard to the actual cautery; and while I think the actual cautery is good, yet one cannot regulate the depth so accurately as can be done with a fine electric needle.

Dr. I. L. McGlasson, San Antonio, Texas: I should like to endorse what Dr. Guy has said. In the thickened cases of leukoplakia, then, we need not hesitate to transfix them with the radium needles. In one case with a vegetative overgrowth which section showed to be nonmalignant, we transfixed the plaques with a radium needle very successfully. I think the difficulty some men get into with a flat applicator is that they give too long an exposure. I do not think it is necessary to give a long exposure to get rid of these patches. I agree with Dr. Corlett that antisyphilitic treatment does not do any good. Whether the leukoplakia is on a syphilitic base in some cases I cannot say, but antisyphilitic treatment does not assist in clearing them up.

Dr. Edwin P. Zeisler, Chicago: I should like to report two cases in which all ordinary methods of treatment were unsuccessful. They were both extensive leukoplakias of the tongue and had been treated by some of our best radium experts. Both patients were referred to the Mayo Clinic and treated by Dr. New by his cautery method under general anesthesia, and the results were remarkable. The thick leukoplastic patches entirely disappeared.

Dr. W. H. Goeckermann, Rochester, Minn.: I do not know the exact method that Dr. New uses, but I know that in some cases he uses the plaque Dr. Guy mentioned. The local treatment is all under his direction. I find that syphilis is frequently present in cases of leukoplakia. Often we find small patches of leukoplakia in the routine examination, when the patient calls no attention to it. Compared with the dermatologic cases, I should say that its prevalence in syphilitic cases is very large, although I do not mean to say that it is syphilitic.

Dr. F. J. Eichenlaub, Washington, D. C.: The chief object in presenting this paper is to try to establish so far as possible the idea that leukoplakia does not always mean syphilis. We are ready to admit that the site of an old syphilitic lesion is more likely to develop leukoplakia, but the field of syphilis is large enough as it is, and I think we should separate definitely those cases that are not syphilitic from those that are. We have had no experience with radium, and it may be good treatment. However, my feeling, and that of Dr. Hazen, is that the cases that are deep and extensive should be left alone and watched for the development of cancerous degeneration.

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A PECULIAR DISCOLORATION OF THE SKIN

PROBABLY RESULTING FROM MERCURIAL COMPOUNDS (CALOMEL) IN PROPRIETARY FACE CREAMS *

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A limited number of drugs and chemicals are known to produce a fixed discoloration when applied to the surface of the skin. Olson [1] has carefully summarized our present knowledge of the localized argyrias. Pusey [2] describes an interesting pigmentation resulting from a solution of the sulphate of iron used in dressing dermatitis. Tattooing is, of course, familiar. The pigmentation resulting from the application of heat and irritating chemicals, such as mustard, cantharides and croton oil, are secondary to inflammatory changes and can usually be readily traced to the offending agent. I have not been able to find any reference in the literature to persistent discoloration resulting from the use of mercurial cosmetics.

Recently, we have had the opportunity to observe two patients with such a pigmentation, resulting apparently from mercurial salts in a face cream.

REPORT OF CASES

CASE 1.—Miss C. A., aged 45, a schoolteacher, who was first seen Dec. 27, 1920, complained chiefly of discoloration of the face and of insomnia. The skin of the eyelids, nasolabial folds and chin and the folds of the skin of the neck were a brownish-gray or slate color. At a distance of several feet, the discoloration reminded one strongly of the

* From the section on dermatology and syphilology, Mayo Clinic.

1. Olson, G. M.: Argyria Localis Due to Organic Silver Preparations, J. A. M. A. 69: 87-90 (July 14) 1917.
2. Pusey, W. A.: The Principles and Practice of Dermatology, New York, D. Appleton & Co., 1917, p. 958.

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dirty neck and face of a boy who has limited his ablutions to Tom Sawyer's minimum. In fact, this teacher's pupils had remarked that she did not wash her face properly, and some of her co-workers had, in a bantering manner, passed similar comments. A well-known dermatologist had told her that he considered the discoloration to be due to a metallic deposit but that he could not identify the source. He had evidently not suspected the face cream.

Inspection with a 10-diameter lens showed that the discoloration of the affected areas was due to minute black puncta in the stomata of the individual glands and in the follicle mouths of the skin. The greater intensity of the pigmentation in certain parts could probably be accounted for by a redundance of the skin and the large size of the glandular openings in these regions.

A painstaking general examination of the patient, including studies of basal metabolism and endocrine function, revealed nothing of note. The patient would not permit a biopsy on the pigmented parts. An attempt was made to gather enough material for chemical examination by scraping the superficial layers of the skin but nothing could be removed in this way. The patient, however, had with her a jar of her favorite face cream, a widely known preparation, which she had used for fifteen years. This was analyzed by Osterberg of the section on biochemistry, and was found to contain large amounts of bismuth and mercury. Owing to the fact that the pigmentation involved only the areas over which this face cream had been applied, and in consideration of the evident superficial character of the pigmentation, it was strongly suspected that one of these chemicals might be the causative agent. Further study of this patient could not be carried out.

Case 2.—Mrs. K. H., aged 31, who was seen for the first time, March 21, 1921, presented virtually the same type of discoloration of the face and neck as that in the patient in Case 1, only the pigmentation was less pronounced. The discoloration of the face had been noticed for about four years. The patient herself had begun to suspect that it was probably due to the face cream she had been using, but believed that part of it was the result of "liver trouble." A general physical examination revealed one infected tooth and some slight tenderness over the gallbladder region, but was otherwise negative. Cholelithiasis was suspected, the opinion being based chiefly on the patient's statement of symptoms.

OBSERVATIONS MADE ON CHEMICALS IN FACE CREAM

A number of experiments were made on this patient. She would not allow a biopsy on the skin, since she could not be assured that there would be no scar. Superficial scrapings of the skin were made, but not

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enough material was obtained for a reliable chemical examination. This patient's face cream was of a different brand from that used by the patient in Case 1. This preparation also was examined by Osterberg, who reported that of active chemicals it contained only mercury, probably in the form of mild mercurous chlorid. This report was confirmed by the patient, who said that she had seen a report of a chemical examination of her favorite face cream in one of the popular journals. The report stated that the cream was a suspension of mild mercurous chlorid. The experiments performed to determine the effect of the face cream on the skin were materially simplified by the fact that the cream contained only one active chemical ingredient. It could thus be argued that its behavior could be attributed to the action of mild mercurous chlorid.

An attempt was made to dissolve the black deposit on the patient's skin by various solvents. Water, soap and water, ether, acetone and dilute acetic acid were used in succession. None of these had the slightest dissolving or decolorizing effect on the deposits. The failure of these agents can be readily understood when it is considered that practically all of the pigment was confined in the glandular openings and probably the ducts and was therefore not very accessible. On several occasions, the cream was applied to the cubital region of the patient's arm under bandages. These bandages were left in place for forty-eight hours, and the patient was requested to take long walks. On one occasion, the patient perspired freely while the cream was in place; the skin was not discolored.

A similar method was followed in order to determine whether the reaction of the perspiration was acid or alkaline. Pink and blue litmus paper was bandaged on the skin instead of the cream. The pink paper always turned a light blue, and there was no change in the blue paper. This suggests that the secretions

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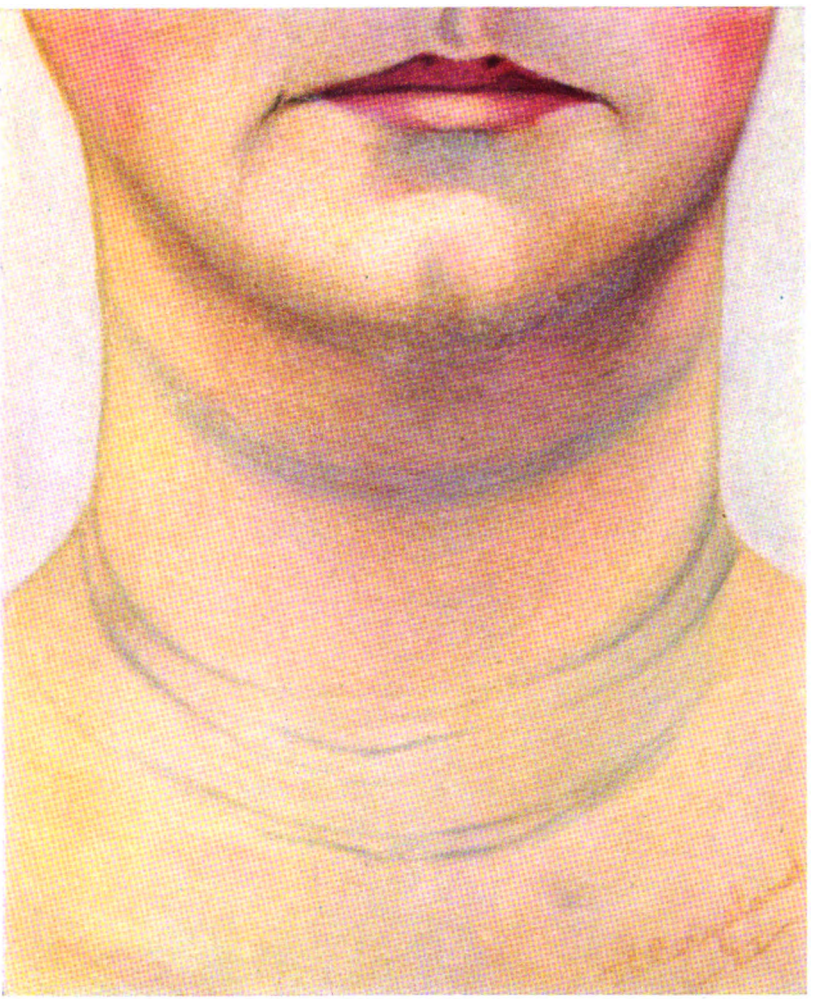

Fig. 1.—Mercurial pigmentation of face from face cream.

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were slightly alkaline. Whether this alkalinity was the sole factor in the production of the black deposit it is difficult to determine. It is impossible to argue that the alkalinity of this patient's secretion was the only factor in the production of the discoloration. Physiologists evidently do not agree on the reaction of the sweat in normal persons. Zuntz and Loewy [3] say that pure sweat is usually acid in reaction, and only occasionally alkaline or neutral. Landois [4] and Stirling express the view that the reaction of sweat is alkaline, although often rendered acid, after secretion, by admixture of fatty acids from decomposed sebum. Either view admits the supposition that our patient had an unusual reaction of the skin secretion, a fact which would explain the comparative rarity of the discoloration.

After applying the cream to my own arm, I made it slightly alkaline with a weak solution of sodium bicarbonate, and it produced a black deposit. Likewise, when the cream was applied to wood and metal surfaces, it yielded the black deposit promptly. It is, of course, well known that mild mercurous chlorid preparations made alkaline rapidly change to the black mercuric oxid and mercury mixture, essentially the old-fashioned "black wash."

Quite as striking as the formation of a black deposit on alkalization was the rapid decoloration when the deposit was made mildly acid. A weak solution of acetic acid was used, and the decoloration which followed can readily be explained by the formation of mercuric acetate.

Thus far our last two experiments had suggested that a mercurial face cream in contact with an alkaline secretion or solution yields a blackish pigment of mercuric oxid and mercury, and that the reaction was apparently reversible by a dilute acid.

3. Zuntz, N., and Loewy, A.: Lehrbuch der Physiologie des Menschen, Leipzig, Vogel, 1920, p. 165.
4. Landois, L.: A Text-Book of Human Physiology, Philadelphia, P. Blakiston's Son and Company, 1891, p. 567.

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BEHAVIOR OF THE DISCOLORATION WHILE UNDER OBSERVATION

When the first patient (Case 1) was seen we did not know the chemical composition of the cream and for that reason we were not able to suggest a rational solvent for the deposit. Hydrogen peroxid was tried for its well-known bleaching properties, but it was without effect.

Three months after the patient's first visit, no appreciable change had occurred, although the use of the cream had been discontinued during this time. Meanwhile, the second patient had been examined, and the behavior of her face cream on alkalization and acidulation had been observed. As the latter cream contained mild mercurous chlorid only, it was assumed that this chemical alone was the offending agent. Therefore, both patients were advised to wash the discolored parts of the skin with a 2 per cent. aqueous solution of acetic acid twice daily. When the patient in Case 1 was seen after a second interval of three months the discoloration had grown materially lighter but was still plainly visible. At that time it was decided to use a 1 per cent. aqueous solution of potassium cyanid instead of the acetic acid solution, because of the well-known ability of the former to form water-soluble double salts with some of the heavy metals, including mercury. Three months after this suggestion had been put into effect, the patient said that the discoloration was constantly growing lighter but had not yet entirely disappeared.

The patient in Case 2 also used the cyanid solution following a trial of the acetic acid solution. She left our observation after about six weeks. The pigmentation was then definitely lighter in color. It should be mentioned that the acetic acid and potassium cyanid solutions used were found to be somewhat irritating to the skin. Solutions of half the strength would probably have answered the purpose.

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It is not especially surprising that the pigmentation should be persistent even when proper solvents are applied. Careful inspection disclosed that the deposit was actually within the gland ducts and therefore relatively inaccessible to a solvent.

COMMENT

After finding mercury in both cosmetic creams, I inquired somewhat more closely into the composition of such creams and found that mercury compounds are freely used in the preparation. The mercuric acid nitrate and chlorid, but chiefly mild mercurous chlorid, are favorite ingredients. The most plausible explanation of the apparent rarity of the discoloration described seems to be that the skin secretions of our two patients present peculiar properties. According to physiologists, an alkaline skin secretion is rare. The alkalinity of the sweat of one of our patients to litmus may explain the occurrence of this type of discoloration. Another explanation of the apparent rarity of the discoloration may be the fact that a woman thus predisposed would discard a mercurial cream at the first sign of darkening of the skin. It must certainly be unusual for a woman who gives the closest attention to her complexion not to suspect her face cream after many years' use of it. Prolonged application of mercurial preparations may be necessary to effect this typical pigmentation, and the practice of changing the brand of face cream frequently may explain the rarity of the trouble. It is quite possible too that the milder grades of discoloration have simply been overlooked.

A final statement as to the exact chemistry involved is probably not justifiable. A number of interesting speculations, however, present themselves. The fact that the mild mercurous chlorid in the face cream so promptly gave a black deposit on alkalization would make me suspect that mercuric oxid is formed, which later deposits metallic mercury. The deposit of metallic mercury in a finely divided state may account

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for the persistent discoloration of the glandular openings. Again, the possibility of unusual bacterial activity on the skin of these patients must not be overlooked.

CONCLUSIONS

1. Mild mercurous chlorid and possibly other mercurial salts may produce a peculiar type of discoloration when persistently applied to the unbroken skin of certain persons. In our patients, the mercurial salt was contained in proprietary face creams.

2. The discoloration may prove a source of considerable diagnostic difficulty even to experts and of much worry to the patient.

3. The pigmentation is probably dependent on some peculiar personal characteristic of the skin secretion. My experiments suggest that a mild alkalinity of the secretion may be the deciding factor.

4. Potassium cyanid in from 0.5 to 1 per cent. aqueous solution is probably the best solvent for the pigmented deposit.

ABSTRACT OF DISCUSSION

Dr. F. J. Eichenlaub, Washington, D. C.: I am not quite clear from Dr. Goeckermann's description as to whether we are dealing with a pigment or a discoloring chemical compound in the skin, and I should like to have him clear up this point. It makes a big difference whether it is simply a pigment or whether it is a mercurial salt or metal deposit.

Dr. Richard L. Sutton, Kansas City, Mo.: Owing to the comparative rarity of this condition, and the frequent use of mercurial preparations in "bleaching" powders and "freckle creams," I believe that the process is a more complicated one than the simple precipitation or formation of mercurous oxid. We have all encountered cases in which contact with the skin of certain persons turned gold jewelry brown or black, phurous acid gas. It is possible that the exhalations or excrepossibly as a result of the excretion of sulphur or of sultions of this material might react on mercurial preparations, with ensuing formation of mercury sulphid in the mouths of the sebaceous and coil gland ducts.

Dr. J. M. King, Nashville, Tenn.: Dr. Sutton has expressed my opinion, and it seems to me that as this discoloration comes on the neck it is due to the preparation, the discoloration being due probably to the sulphur compounds secreted by

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the sweat glands or sebaceous glands, forming a black sulphid.

Dr. Ernest D. Chipman, San Francisco: I recall one patient who had several pigmented areas on the face which, to my surprise, were entirely removed simply by the application of alcohol. Doubtless some precipitate, resulting from the promiscuous use of cosmetics, had formed in the skin. This, being soluble in alcohol, was removable.

Dr. Erwin P. Zeisler, Chicago: It might be interesting to recall that lead can be absorbed through the skin in sufficient quantity to cause toxic symptoms. Two fatal cases have been reported of lead poisoning from face creams.

Dr. W. H. Goeckermann, Rochester, Minn.: As to the rarity of this condition, I am not sure that it is so rare. Since preparing this paper I have seen another patient of the same type, and that makes three in a year. Prior to that I had not seen this pigmentation. As to whether it is a deposit or a discoloration, I do believe that there is a certain amount of chemical deposited in the stoma of the gland that produces the pigmentation. It seemed to me that it was a pigmentation, although I believe it was due to a chemical deposit, and so far as I was able to determine the form, it was a mercuric oxid and metallic mercury mixture rather than the sulphite of mercury.

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INDUSTRIAL DERMATITIS AT THE MASSACHUSETTS GENERAL HOSPITAL*

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The papers of Fordyce,[1] Hazen,[2] Knowles,[3] White[4] and Pusey[5] have already pointed out the many occupations in which an irritation of the skin may be produced. They have described the types of eruption appearing as a result of employment in these various occupations, and have discussed the etiologic factors which have caused these irritated conditions. Of particular value is the paper of Knowles, based on the study of more than 7,000 cases of eczema, which was presented in this city just ten years ago this month. A study of his paper, and of the other papers as well, emphasizes the importance of external causes in the etiology of these pathologic skin conditions. These authors have made a distinct contribution to our knowledge of such dermatoses, and rendered a real service to dermatology and to the afflicted patients.

But have we profited by this knowledge which they have given us? Have not their lessons been relegated to the background in the

* From the Dermatological Clinic, Massachusetts General Hospital.

1. Fordyce, J. A.: Occupational Diseases of the Skin, M. Rec. **81**:207 (Feb. 3) 1912; Occupational Skin Diseases, J. A. M. A. **59**:2043 (Dec. 7) 1912.

2. Hazen, H. H.: Industrial Skin Diseases, J. Cutan. Dis. **32**:487 (July) 1914.

3. Knowles, F. K.: The External Origin of Eczema, Particularly the Occupational Eczemas, as Based on a Study of 4,142 Cases, J. Cutan. Dis. **31**:11 (Jan.) 1913; Eczema of External Origin, and Its Relationship to Dermatitis, J. A. M. A. **68**:79 (Jan. 13) 1917.

4. White, C. J.: Certain Occupations as Contributing Factors to Diseases of the Skin, Boston M. & S. J. **175**:35 (July 13) 1916.

5. Pusey, W. A.: Industrial Dermatoses, Their Sources, Types and Control, J. Indust. Hyg. **1**:385 (Dec.) 1919.

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mass of dermatological literature of the last few years? For instance, are we not likely to forget the frequency with which occupational cases are appearing in our clinics? Fordyce has stated that 2 per cent. of the total number of new cases at his skin clinic for 1911 constituted occupational dermatoses, and Knowles in 1913 and 1917 estimated that one sixth of all eczema was due to occupation. There is no doubt that at least the same percentage of our skin cases today will be found by careful study to be due to occupational factors.

In this paper it is my purpose to act as the social service worker, that is, to attempt to do a little "follow-up work," and help "carry on" in this broad field in which these pioneers have shown the way. I shall discuss the occupational cases appearing at the Massachusetts General Hospital in the last few years, and emphasize the opportunity presented to us, as dermatologists, to contribute a still greater share to the work of preventive medicine.

In making this study of the cases of occupational dermatitis, it was found that no attempt had been made to group these cases in the diagnosis catalogue. Experience in the clinic had shown that the majority were given a diagnosis of dermatitis, dermatitis venenata or eczema. It has been necessary, therefore, to examine all records with the foregoing diagnoses in order to find the cases associated with the patient's occupation. For the three years 1919, 1920 and 1921, there were 921 cases of dermatitis or dermatitis venenata treated in the oupatient skin department. A critical examination of these records revealed 106 cases in which the occupation was a probable etiologic factor. In more of these cases the relation was not as clear cut and the evidence did not warrant including them in this group. In other words, there were 11.5 per cent. of the cases of dermatitis or dermatitis venenata which were probably industrial in origin.

In a similar manner, the 1,086 cases of eczema for the years 1920 and 1921 were examined. In this group there were forty-eight cases in which there was definite evidence on the record to show that the skin condition was probably derived from the patient's trade or occupation. There were, then, 4.4 per cent. of the cases of eczema from industrial causes.

The accompanying table shows the number of cases occurring in each year and the number of patients admitted to the skin department for each year.

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NUMBER OF CASES AND NUMBER OF ADMISSIONS

	1919	1920	1921	Totals
Admissions to skin department	2,263	2,301	2,580	7,144
Cases of dermatitis	249	365	307	921
Cases of occupational dermatitis	22	47	37	106
Cases of eczema	....	522	564	1,086
Cases of occupational eczema	....	25	23	48
Total cases of dermatitis and eczema	249	887	871	2,007
Total occupational cases	22	72	60	154

For the year 1921 there were sixty occupational cases among 2,580 admissions to the skin department, so that the ratio of industrial cases to total admissions, so far as it is possible to ascertain, was 2.3 per cent. The ratio in 1920 was 3.1 per cent. The cases of eczema in 1919 have not been studied, but it is hoped to make still further investigation on this subject.

In the two years 1920 and 1921 there were 132 cases which were caused by occupational conditions. This is 7.1 per cent. of all cases of dermatitis, dermatitis venenata and eczema, or 2.7 per cent. of the total admissions to the skin department.

From a study of these records I feel that the actual percentage is larger than these figures show because of the number of cases, especially of eczema, in which the occupational factor was not mentioned. Furthermore, burns, infected conditions, keloids, etc., have not been examined from this point of view. I believe that it would be a conservative estimate to say that 4 or 5 + per cent. of the admissions to the skin clinic may be caused by occupational factors.

Examination of these 154 cases more closely shows that there were ninety-four, or 61 per cent., male, and sixty, or 39 per cent., female workers, all of them white. The ages varied from 16 to 82 years. Housework and allied work contributed forty-seven, the greatest number, to the group. Various washing powders, naphtha soap, soapine and brass polish are the agents most frequently mentioned as the exciting causes. Seven men are included in this group, their occupations providing opportunity for contact with washing powders and cleansing agents. The shoe workers, fourteen in all, formed the next largest class. There were twelve who handled dyes in some form or other. Paints, including furniture polish and varnish and various removers, accounted for ten. There were seven rubber workers, and seven who

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worked in candy factories, four of the latter among chocolate workers. There were six nurses in the group, and three men in whom cyanid was a probable factor. Among the others, the following types of workers were represented: machinist, photographer, silver polisher, packers (using hay, straw, etc.), baker, tanner, cement worker, nickel plater, tobacco worker, longshoreman, bleacher, upholsterer, waitress, gardener, necropsy room attendant, miller, acetylene worker, labeler, lumberman, farmer, wool worker and printer. A more detailed investigation of these cases is being undertaken, and a further report will be made in a later paper.

The investigation of these cases has been greatly facilitated by the industrial clinic at the Massachusetts General Hospital. This is a separate clinic through which pass all cases of disease associated with industrial conditions, or any condition suspected of being associated with an industry. This clinic is one of the first, if not the first, industrial clinic established in a general hospital. This clinic has a very close association, on the one hand, with the department of industrial hygiene in the Harvard Medical School, and, on the other hand, with the state department of labor and industries, and through the latter with many factories and manufacturing establishments in the state. It therefore offers an opportunity for the scientific study of occupational diseases, and also an opportunity for an accurate investigation of the conditions under which the disease or condition may have been acquired. It is possible, then, for a patient with an industrial skin condition, or one suspected of being such, to be referred to this clinic for investigation. This clinic will interview the patient, and report the case to the state department of labor and industries, which will send out an inspector to investigate the particular plant and the particular part of the work which this patient does. Furthermore, this clinic is in position to follow up the patient to make sure that he returns to the skin clinic at proper intervals for treatment; to attend to various details in connection with compensation, if time is lost, and to maintain close cooperation with the various industrial physicians in the vicinity.

METHOD OF DEALING WITH DERMATOSES

The study of these cases has brought home to me very forcibly several facts which seem essential in the proper dealing with these dermatoses. In the first place, there is the wide variety of occupations

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in which a dermatitis may arise. The list which I have given discloses some of the types of work, but there are many others to which our attention has already been called. In the second place, there should be a more careful study of the patient. These occupational cases are likely to be lost in the rush of the clinic. They are likely to be considered as an ordinary type of skin disease, for they do not usually present unusual and therefore interesting manifestations. Some present the picture of an acute dermatitis of short duration. Others simulate an eczema of long standing. Others appear as burns, boils, etc., or as other common conditions. We are likely to write a few words of description on the record. We make a diagnosis of acute dermatitis, dermatitis venenata or eczema, or the like, and we prescribe some simple remedy for the relief of the present condition. Often, in the crush of the clinic, little thought is given to possible occupational factors, and still less attention is paid, I am afraid, if the patient is unable to understand or speak good English. The patient is dismissed to make way for the next one without an attempt to study the case or the working conditions. Let me use, as an example, certain cases of eczema in 1920, ninety-nine in all, in which the disease was practically limited to the hands and arms. In fifty-two of these the occupation was given as "housewife" or "at home." There was no indication on the record that the occupation of any of this group had been considered as a possible cause, and I have not included these among the occupational cases. But I believe that many of them were due to some element in their work. Such cases are lost, not only for the purpose of statistical study, but also for the purpose of investigating the industrial factors involved, and without the knowledge based on the study of such accumulated facts it is a difficult matter to take steps for the prevention of such skin conditions among susceptible persons.

In the third place, there should be a more exact analysis of the job, and a wider knowledge of trade processes and conditions. Pusey has already emphasized the necessity for "more knowledge of the factors which are important in the production of these diseases and in their prevention and control." It is not enough to know that a man is a painter or tanner or dyer or rubber worker. We should find out the active agent in producing his condition, or at least instigate an investigation of his working conditions, of the substances which he handles and of the effect of such factors on the skin. The fact that

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a man, aged 33, with an eruption on his arms, is a night pumper in a compressed gas factory means little till it is found that at intervals during the night he fills a generator with calcium carbid, wearing only cotton gloves. The same is true of the book packer who is found to handle new books and to have his hands become covered with stains from the covers, or the housewife who is working part of the time in a tobacco factory as a stripper, or the jeweler working with cyanid in the coloring room. The exact knowledge obtained in the study of the processes of vulcanizing and of printing has been of inestimable value in the proper handling of the dermatoses occurring in these occupations. A most valuable feature of the book on this subject by R. Prossner White [6] is the detail with which the trade processes are explained.

In the fourth place is the fact that the prevention of these dermatoses should receive greater emphasis. There is, of course, the present skin condition to treat; but the real problem is the prevention of its recurrence and the prevention of a similar condition in other susceptible persons. The situation is analogous to the infectious skin conditions. We do not make a diagnosis of scabies or impetigo without taking steps for the prevention of its recurrence and for preventing the infection from appearing in others; but meanwhile we treat the existing condition. The same should be true in the case of the occupational dermatoses—the proper treatment should mean prevention.

We need, first, to realize the wide variety of substances responsible for these skin conditions; then to make a painstaking inquiry into the individual case, and to make a careful analysis of the work he is doing, and on this foundation attempt to build a rational procedure for his particular kind of work. There has been exact scientific work of this character in the last few years in the study of two occupations, and it seems reasonable to expect that further similar studies will eliminate the skin conditions resulting from other trades. I assume that most readers are familiar with the preventive work which has been done in the case of the vulcanizers and among the pressmen in the printing trade, but the importance of this research work warrants a brief review.

Among the vulcanizers it had been noted that eruptions appeared on the forearms and hands of men using hexamethylenamin as one of

6. White, R.: Occupational Affections of the Skin, Ed. 2, New York, Paul B. Hoeber, 1920.

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the accelerators in the vulcanizing process, especially in hot weather. Working on the theory that under the influence of the acid in the sweat the hexamethylenamin was broken down to formaldehyd, and later oxidized to formic acid, and thus causing an irritation, Shepard and Krall [7] used alkaline solutions for the immersion of the hands and arms of susceptible persons previous to going to work, and found that the condition did not appear.

Among the pressmen there were a number of workers with an eruption on the exposed surfaces. McConnell,[8] after a careful study of the working conditions, inks, cleansing processes, etc., found that by applying a mixture of lanolin or lanolin and oil before working, and by using a liquid soap and sawdust for cleansing purposes, the eruption could be prevented.

In both of these occupations the result was obtained by changing the working conditions without changing the man to another job. It is interesting to note that the first report issued by the committee which studied the eruptions among the vulcanizers recommended a change of work; but the later investigations made this unnecessary. This is the usual suggestion made in the treatment of these dermatoses. It is well to remember that there are the two possibilities, in this phrase, one to send the patient to another job, and the other to alter the process or the working conditions in some way. The former is the one usually employed, thus allowing the conditions to remain for the next susceptible person. It is not hard to imagine the difficulty with which a person acquainted with only one kind of work adapts himself to another kind, especially if he has worked at the first one all his life. The most rational preventive measure, then, is the one directed toward rendering the working conditions as safe for the susceptible workers as possible.

The study of these occupational cases emphasizes still further the fact that these persons with eruption caused by their work have undoubtedly become sensitized in some way to a particular substance, or that they are naturally susceptible. At any rate, to be still more indefinite, they are cases of idiosyncrasy or individual susceptibility. The fact so often used in arguing against these cases, that the condition

7. Shepard, N. A., and Krall, S.: Poisons in the Rubber Industry, India Rubber World **61**:75 (Nov. 1) 1919.

8. McConnell, W. J.: Industrial Dermatosis Among Printers, Pub. Health Rep. **36**:979 (May 6) 1921.

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cannot be due to the occupation because the one person affected is the only one in his room, or the only one affected among many who are using the same substances, or working under the same conditions, is no argument at all, of course. It is perfectly possible for only one person out of fifty or a hundred to have an eruption from handling dyes, or to be the only one out of a large gang of machinists who will be affected by oil, etc. I emphasize this fact because only recently before the industrial accident board an employer defended his case by bringing in man after man employed in the same process as the patient and exhibiting them to the board as examples of the fact that the process did not cause any irritation. The case was one of undoubted susceptibility, and yet the board, at last reports, had decided in favor of the employer. Moreover, the same fact is true in these cases that is true in cases of food sensitization, or of suspected food sensitization, because of positive cutaneous reactions; namely, that only a therapeutic test—the matter of omitting a certain food from the diet in one case, and the matter of omitting a certain process or a certain substance in the other case—is the only real test. It is also important to remember in this connection that there are cases of individual susceptibility to extremely minute quantities in the cases of foods and drugs, and that undoubtedly the same fact is true in connection with these occupational cases.

Finally, the very number of these fairly definite occupational skin conditions suggests the advisability of grouping these cases better for the purpose of statistical and preventive study. Can we not call attention to these dermatoses in a more forceful manner? Would it not help to emphasize them by giving them a more definite place in our official nomenclature? We have the term dermatitis medicamentosa applied to dermatoses from the absorption of medicinal agents. Why can we not adopt some term, such as "dermatitis industrialis" to be applied to this group of pathologic skin conditions resulting from the industry in which the patient is employed? The name "trade eczema" has the advantage of long usage, but it seems as if the time had come when we ought to cleave these cases of occupational skin conditions from the eczema group and segregate them in a group by themselves. One objection immediately raised is in regard to the multiform character of the lesions caused from various substances. The possible multiformity is apparent; but, as one thinks of dermatitis venenata with its erythematous, papular or vesicular lesions, and of dermatitis

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medicamentosa with its macular, papular, pustular or verrucous lesions, such objections seem inconsistent. These are examples of a definite etiologic group, but with possible multiform appearance. The importance of this group in the economic and financial life of the employee who suffers such disability, and the loss in efficiency with the consequent financial loss to the employer, serve as an additional argument for the use of a definite name. If some term, such as "dermatitis industrialis," cannot be agreed on, let us at least adhere to the term occupational dermatitis, or agree to group these cases under one or the other of the diagnoses dermatitis venenata or eczema, and use the term occupational as a qualifying phrase, in order that they may be available for proper study.

CONCLUSIONS

1. Seven per cent. of dermatitis venenata and eczema, or almost 3 per cent. of all admissions to a skin clinic in a large hospital, were occupational in origin.

2. It is fair to estimate that 4 or 5 + per cent. of admissions to a skin clinic may be occupational.

3. A more careful study should be made of the individual patient.

4. A more exact study of trade processes should be instigated in case of questionable eruptions on exposed surfaces.

5. The consideration of preventive measures should be a greater factor as we see these cases in the clinic.

6. Some name, such as "dermatitis industrialis," or at least a more accurate place in our nomenclature, should be provided for this definite etiologic group of cases.

421 Marlborough Street.

ABSTRACT OF DISCUSSION

Dr. Richard L. Sutton, Kansas City, Mo.: I wish to thank Dr. Lane for his suggestion of the term, "dermatitis industrialis," for it fits these cases admirably. I also wish to recommend to my fellow dermatologists a splendid little book along this line, "Occupational Affections of the Skin," by R. Prosser White. It is one of the most useful volumes in my library. I found it almost encyclopedic in its scope.

Dr. Joseph Grindon, St. Louis: Attention has been particularly directed during the last several years to the importance of the subject of occupational diseases, and yet there remains a good deal to be learned in regard to occu-

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pational dermatoses. In the first place, what shall we call them? Certainly not "trade eczema." When the causative agent is determined we arbitrarily take the disease out of the "eczema" group and place it in the dermatitis group. The term "trade dermatoses" would be unobjectionable. There are several things to bear in mind in connection with these cases. First, we know only a small part of the subject, and we should all be on the lookout for new forms. Not only in our clinics but in our private practice we often forget to inquire into the occupation of the patient whereas often the occupation would throw a light on the condition. These conditions sometimes lead to damage suits. There are some cases of malingering. Other cases are exemplified by that of a man with a congenital ichthyosis, which he attributed to his trade. Again, there are cases in which the patient honestly but erroneously believes that an eruption is due to something connected with his occupation. I recently saw a man who took a new job on Saturday. On Sunday he went out picnicking and Monday developed a toxicodendron dermatitis, which he honestly thought was due to his trade. At the same time we must be ready to do the patient full justice and not hastily determine that the condition is unconnected with his occupation when, perhaps, we are insufficiently informed. If we gave a little more thought to a matter spoken of by Dr. Lane, namely, special sensitization, we sometimes would feel that there was more in the contention of the employee. The responsibility of the physician is great. He should make it a matter of conscience and thoroughly consider the question before giving a decision.

Dr. Jeffrey Michael, Houston, Texas: I would like to add to the long list of industrial dermatoses another which occurs in the oil fields, due to crude petroleum. It has no clear-cut clinical features, except that the covered portions of the body are more affected than the uncovered. This is due to the fact, I think, that the clothing is saturated with the irritating oil.

Dr. Moses Scholtz, Los Angeles: This subject interests the dermatologist as he is called on to determine whether the patient is entitled to compensation or not. The hardest thing I find is to tell when the condition is ordinary eczema and whether it is systemic in origin or occupational. Whether we call it "eczema" or "dermatitis," the conditions are identical conceptions. It is simply a difference in nomenclature. I tried to differentiate morphologically, and my impression is that toxic eczema is likely to be less symmetrical than the occupational variety. Systemic eczemas are likely to affect any portion of the body while the occupational variety is most likely to affect the face, neck or hands. We often see the hands free, and we then have to assume dust or irritation through the air rather than direct contact as a cause. Another point is that the systemic eczemas are more likely to be fluctuating in their course, while those due to external irritation are likely to be more stable. If any one could give us a definite morphologic differentiation of systemic eczemas from those due to external irritants, it would be of great service.

Dr. T. J. Burke, Pittsburgh: I wish to call attention to a preparation in relation to these dermatoses, that known as "Lux." It is much used for

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washing shirt waists and other garments of that kind. There is nothing on the label or the instructions regarding its use to lead one to think that there is any danger in using it, but I have seen a number of cases in which it had caused a severe dermatitis.

Dr. William Allen Pusey, Chicago: Dr. Lane touched on one point lightly—the necessity of a more intensive study of these occupational dermatoses. The great difficulty is that the industrial physician or surgeon is interested in other things and is not a trained dermatologist. What is needed, and what I believe is a possibility if it is gone after, is to get some of the foundations, or perhaps the U. S. Public Health Service, to make a real study of this condition. I know that young well trained dermatologists are in great demand, but I still think it is possible to have two or three of the young, well trained men devote their time to this question for two or three years. They could take with them some of the nestors of dermatology. We could be of help as consultants.

Dr. C. H. Ball, Tulsa, Okla.: My impression is that the main thing in a dermatitis is the peculiar idiosyncrasy of the individual. In a large establishment only a few men will have a dermatosis following an irritation of the skin. Possibly one of the worst cases I have ever seen was treated here in St. Louis by a well known dermatologist as dermatitis exfoliativa, and it was due entirely to a well known brand of hair dye.

Dr. S. Ayers, Jr., Los Angeles: I reported six cases of scleroderma with arsenic in the urine. Dr. Sutton had one of these cases. The history in several of the cases was very suggestive of an industrial dermatosis. One of these patients worked in a paper factory and examination of several samples of that paper showed a high content of arsenic. I think this is against the law now, but it is used nevertheless. Another one of the patients, a woman who kept a grocery store, used powdered arsenic in a dish under the counter for killing mice. The duration of her disorder was coincident with the use of the powder.

Dr. Lester Hollander, Pittsburgh: During the last year I treated four severe cases of vesicular dermatitis, affecting the hands and forearms, and in one instance spreading to the face, in workers in the photographic trade. After careful investigation I was able to determine that metol, which is used in the developing of photographs, was the offending agent. The chemical used was manufactured by the same concern in each instance. As I had a great deal of difficulty in clearing up these lesions, I communicated with the Eastman Kodak concern of Rochester, N. Y., regarding the necessity of medical investigation of industrial dermatoses. In this particular instance the industry itself had taken up the problem. Regarding the treatment, two things must be considered, especially when we are speaking of the acute type of trade dermatoses, the treatment of the condition itself and the prevention of its return.

Dr. Sutton mentioned the fact that simply removing the patient from his work does not mean that the dermatologic condition is cured. I heartily

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endorse that view. Regarding the view of some writers that trade dermatoses depend on idiosyncrasy, in the four cases mentioned skin tests were utilized for the determination of the causative agent, but only two of the cases showed an erythema to metol applied in the form of a skin test. This makes one think guardedly how much of a factor idiosyncrasy really is in trade dermatoses.

Dr. A. J. Markley, Denver: It should always be borne in mind that the irritants with which one comes in contact in industrial occupations constitute only one of the factors in the production of these dermatoses. We know that each person has a certain amount of resistance, and when that resistance is broken down by internal conditions improper diet or focal infection, it requires only a little external irritation to produce a dermatitis. It seems to me wholly unjust that a dermatitis involving the hands and face or considerable parts of the body should be attributed entirely to an external irritation when that irritation is simply the precipitating factor. It is not just to the patient that he should be dismissed with simply an amelioration of the condition from which he suffers. It is not fair to the patient and certainly not to the employer that the occupation be held wholly responsible for having induced an industrial dermatosis, and it is proper that we investigate the personal conditions of diet and of health of these patients. It has been pointed out that only one of fifty employees may have such a reaction, and it has also been pointed out that removal from his work frequently fails to result in complete amelioration or disappearance of the symptoms. Unless we are prepared to inquire carefully into the entire condition, the internal cause as well as the external, we are not doing justice to the industry, to the patient, to the employer nor to ourselves.

Dr. David Lieberthal, Chicago: I want to stress the point that we should not say "occupational dermatitis" but "dermatoses."

Dr. C. Guy Lane, Boston: I did not talk about the occupations listed, but in my group there were thirty-one. I also wish to emphasize the careful scientific work done by the investigator of these two particular trades, among the vulcanizers and the pressmen. Dr. Sutton spoke of the book of Prosser White. I think it is particularly good in the way in which he explains the trade process. The malingerers have been spoken of and also the fact that all dermatoses appearing in workers are not industrial in origin. That must be taken into account every time. Dr. Pusey has brought up the necessity of studying, and I think we should certainly attempt to clear up these conditions. It was my intention to advocate the use of the the term "occupational dermatoses," in this group, but on talking it over with a member of the hospital nomenclature committee, there was some difficulty about including it among the other Latinized names and the term "dermatitis industrialis" seems very apropos. Someone mentioned the use of skin tests, but my experience with skin tests is that this is not a real test of susceptibility in these cases. The real test is the therapeutic test. Having the man stop his work for a period or changing the process proved the cause of the dermatitis better than any skin test can do.

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PITYRIASIS RUBRA PILARIS—FAMILIAL TYPE*

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Pityriasis rubra pilaris was first described by Devergie,[1] in 1857, as "a disease characterized by scaly and horny productions situated chiefly in the sebaceous follicles and by a more or less generalized cutaneous hyperemia." Later Besnier and Richaud described the same clinical condition under the name of pityriasis pilaris. The disease is today generally accepted to be identical with Hebra and Kaposi's lichen ruber acuminatus. The points of identity of the two were recently brought out in an admirable paper by Feldman.[2] Among American authors cases have been described by Taylor, White, Robinson, Zeisler,[3] Ravogli, Heidingsfeld, Shields, Markley and Levin. Nothing definite is known about the pathogenesis. The disease usually begins in early life and persists with occasional exacerbations and periods of remission. Although Hebra's cases terminated fatally, most cases observed in this country have been relatively benign. The particular interest that prompts the present report is the observation of four cases in one family, which occurred in a father and three children. This is the first instance of the familial occurrence of the disease noted in this country, although there are two reports of a similar nature from the continent. The subjoined report is given as added evidence that heredity plays a rôle in the etiology of this rare condition.

REPORT OF CASES

CASE 1.—H. K., a man, aged 46 years, had had a cutaneous eruption since early childhood. The patient was presented before the Chicago Medical Society

* From the department of dermatology, Northwestern University Medical School, and the skin and venereal service, Cook County Hospital.

1. Devergie: Traité pratique des maladies de la peau, 1857, Ed. 2, p. 454.
2. Feldman: J. Cutan. Dis. 1919, p. 227.
3. Zeisler: Chicago Med. Rec. **16**:533, 1899.

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in 1899, by the late Joseph Zeisler, as having a typical example of pityriasis rubra pilaris. A brief description appeared in the *Chicago Medical Recorder* as follows: "The patient, at this time aged 23, presented large areas of erythroderma; branny desquamation in many of these places, exaggeration of the natural folds and furrows of the affected regions, horny punctiform blackish plugs on the dorsal surface of the hands, chiefly the first phalanges, and also ulnar side of the back of the hands corresponding to the follicles of lanugo hairs; hyperkeratotic scaly patches over the knees and elbows. There was no itching and the mucous membranes were free." A report on the pathology of the condition by Dr. Pardee at this time confirmed the diagnosis. Treatment consisted largely of local medication and injections of pilocarpin. The disease gradually improved and for the last twenty years has been so mild as not to interfere with his occupation. In 1902, the question of marriage was discussed. The patient was assured that it was perfectly safe for him to marry as there had been no report of a hereditary transmission of pityriasis rubra pilaris up to this time. Of four children born within the next ten years, three developed the disease during the first year of life.

Examination revealed a healthy, well developed person with normal physical and blood findings. Examination of the skin revealed slight, but unmistakable, evidence of pityriasis rubra pilaris. On the scalp was a branny erythroderma, with involvement of the ears. The face, chest and back were entirely free. There were scaly rough plaques, chiefly on the extensor surface of the arms below the elbows, and characteristic black "plugs" on the dorsal phalanges and backs of the hands. On the lower extremities were oblong red scaly patches over the knees and on both sides of the calves. The palms and soles showed a diffuse thickening with traverse striations of the nails. There were no subjective symptoms.

Case 2.—M. K., a boy, aged 12 years, had had a cutaneous disorder since early infancy. With the exception of diphtheria and scarlet fever at the age of 4, and measles at 6, his medical history was uneventful. He complained of slight itching in winter and a drawn feeling about his face. The skin of his hands cracked and bled easily in cold weather. During the summer the condition improved and the lesions almost disappeared.

A careful physical examination revealed no evidence of organic disease. The boy was well developed and bright. The tonsils were small and buried. There were small cervical and axillary glands. The thyroid was not enlarged and there was no retrosternal dulness. The genitalia were normally developed. There was no physical evidence of endocrine disturbance.

Case 3.—S. K., a girl, aged 16 years, had always been healthy with the exception of measles at the age of 4. She complained of difficulty in breathing, especially on exertion, which she thought was due to adenoids and enlarged tonsils. The cutaneous disorder began shortly after birth and had gradually improved from year to year, with exacerbations in the cold weather. Pruritus was negligible. Menstruation began at 14 and had been irregular.

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Examination revealed a well developed girl with a tendency to adiposity, a full rather slow pulse (60 to 65) with respiratory dyspnea even while at rest. The positive physical findings included the following: A fissured tongue, enlarged cryptic tonsils, cervical adenopathy, a fairly large soft thyroid, slight cardiac enlargement without murmurs and dulness over the upper sternum on percussion. A roentgenologic examination showed a mediastinal shadow which was interpreted as a probable thymus hyperplasia, although a retrosternal thyroid was also considered. The lungs were normal.

Case 4.—H. V., aged 14 years, a sister of the foregoing patient, had had the cutaneous disease in mild form since she was 1 year old. With the exception of a diffuse goiter, large tonsils and a geographic tongue, examination was negative. Another younger child was examined, but presented no evidence of cutaneous disease, and the mother was likewise unaffected.

Laboratory Findings.—The blood findings in Cases 2 and 3 were: an average hemoglobin estimation of 95 per cent.; leukocyte count, 6,500; red blood count, 5,200,000; differential count: polymorphonuclears 77, small mononuclears 19, large mononuclears 3 and eosinophils 1. The blood pressure in Case 2 was: systolic 115, diastolic 85; in Case 3: systolic 110, diastolic 85. Chemical examination of the blood in Case 3 showed a total nitrogen content of 2,560 (normal 2,650), urea nitrogen 9.6 (normal 10), urea 23.5 (normal 21.4), uric acid 1.9 (normal 1.8), and creatinin 1.4 (normal 1.35). The urine findings were negative in all cases.

Cutaneous Lesions.—The eruption in all three children was so strikingly similar that a single description will suffice. The scalp showed a diffuse redness with branny desquamation. The hair was not excessively dry, and there was no alopecia. The cheeks, forehead, nose and ears showed a shiny seborrheic type of inflammation with exaggeration of the lines of the skin. On palpation the affected skin was thickened, inelastic and rougher than normal. The lower lid in one case (Case 2) was slightly everted. At the lower border of the neck the erythroderma terminated abruptly in a sharply demarcated border. There were a few small scaly lesions over the upper part of the chest, but otherwise the trunk was free. The arms presented variously sized scaly, grayish-red plaques of a psoriasiform appearance, chiefly affecting the exterior surfaces around the elbows. On the wrists and back of the hands were rough erythrodermic patches made up of scale-covered conical papules, some of them pierced by hairs, with marked exaggeration of the normal lines. In only one of the cases (Case 2) were found the "black" punctiform plugs which are so characteristic of the disease. These were present on the dorsal surface of the wrists and to a lesser extent on the phalanges. The palms showed a diffuse thickening. The nails were not affected. The lower limbs presented confluent scale-covered patches with islands of normal skin intervening. The nutmeg grater feeling was very apparent on palpation. The knees, thighs and buttocks presented oblong, irregular plaques. Below the knees, extending over the dorsum of the feet, the scaling and roughness was more marked and suggested

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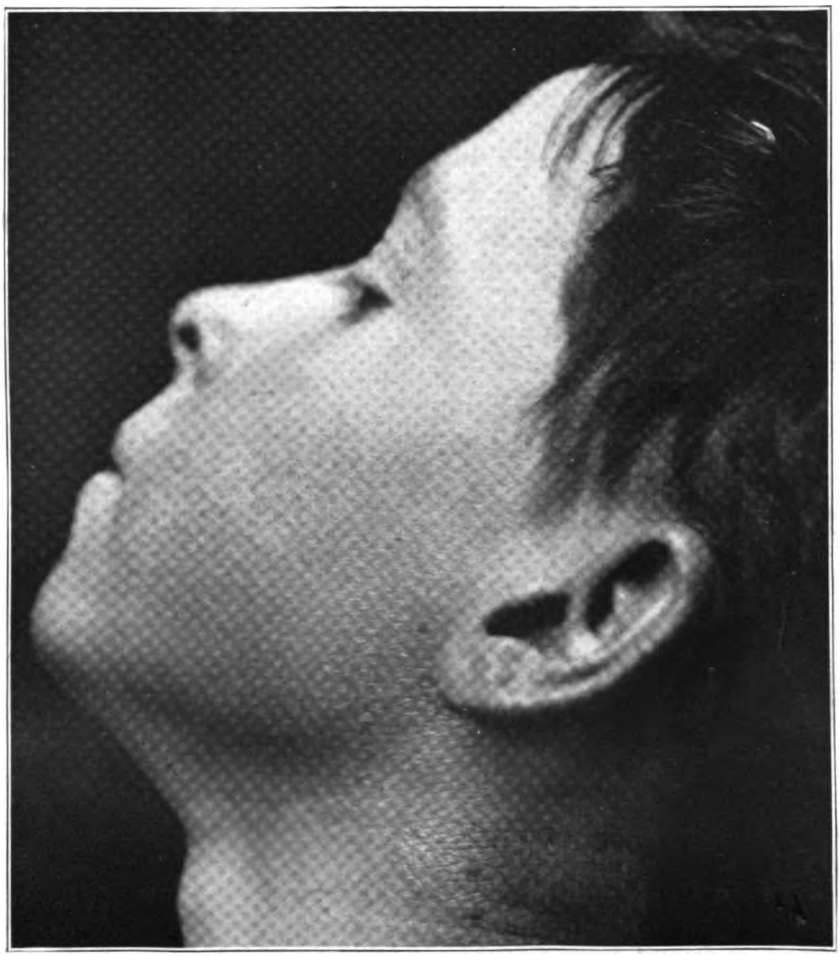

Fig. 1.—Lesions on face of patient in Case 2.

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Fig. 2.—Lesions on extremities of patient in Case 2.

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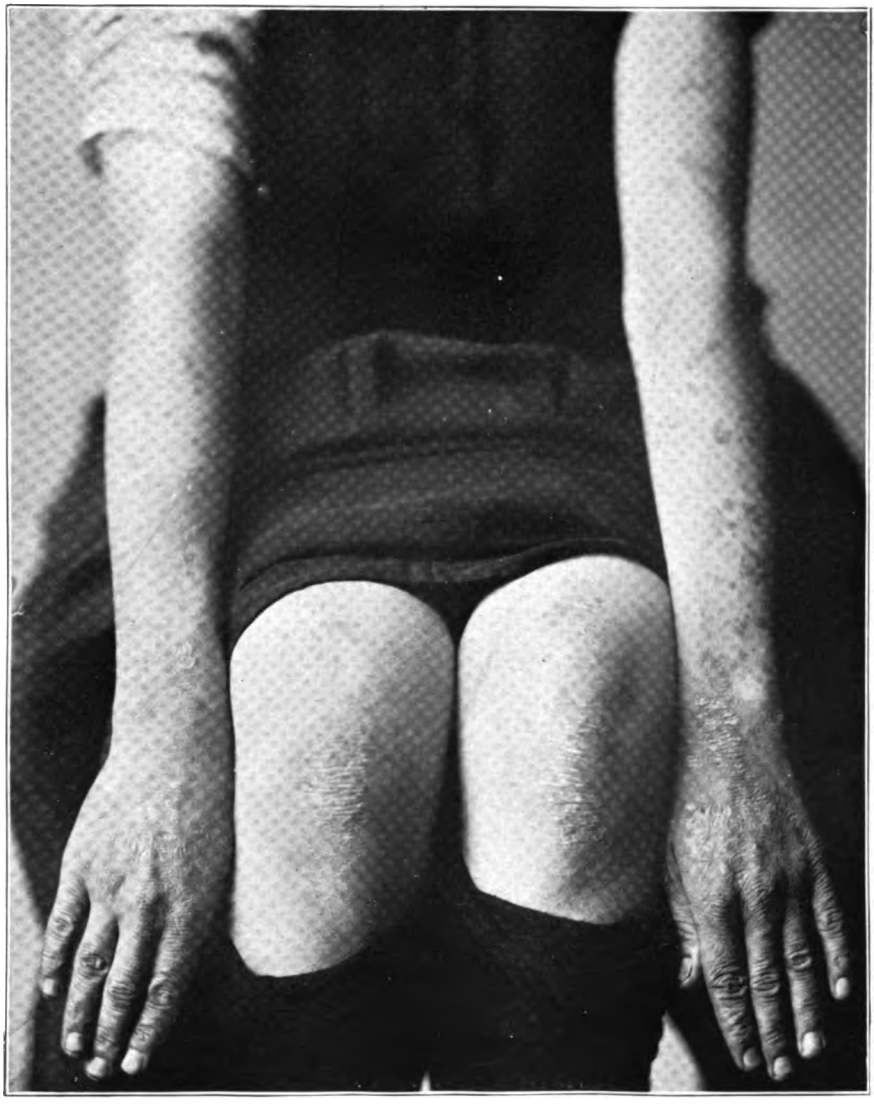

Fig. 3.—Distribution of lesions of patient in Case 3.

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Fig. 4.—Section through horny spine on dorsal phalanges, showing mass of cornified epithelium within hypertrophied follicle.

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Fig. 5.—Section showing corneous plug with embedded hair in dilated pilo-sebaceous orifice.

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Fig. 6.—Section showing double horny pearl in epidermis.

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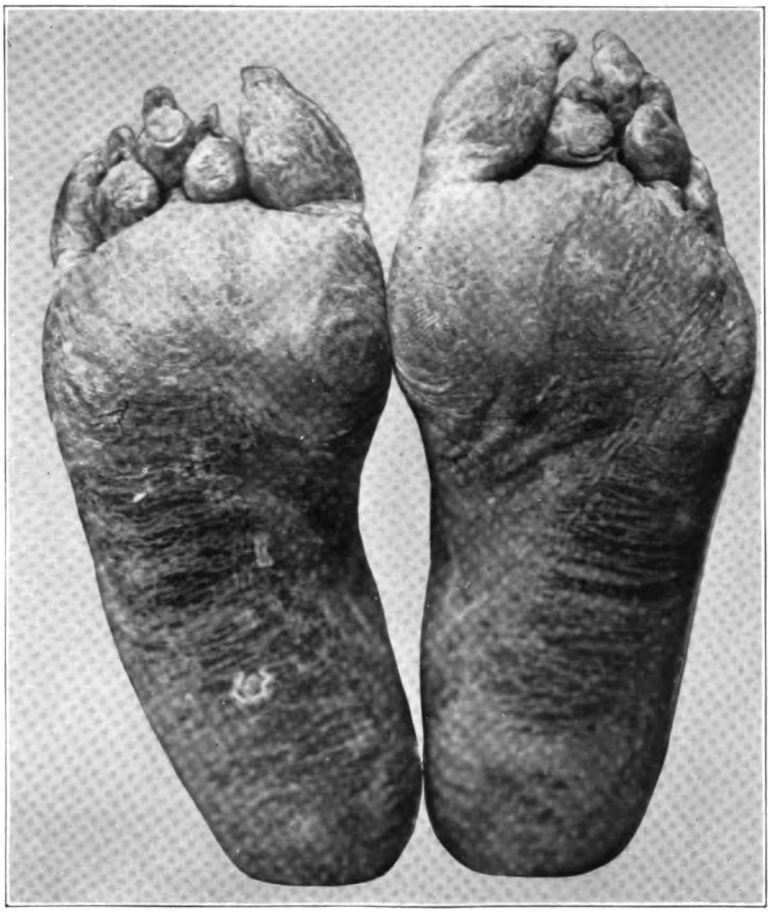

Fig. 7.—Plantar hyperkeratoses with nail changes in a severe case of pityriasis rubra pilaris.

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an ichthyosis. The soles showed a diffuse hyperkeratosis with numerous furrows. The toe nails were thicker than normal. The eruption was everywhere remarkably symmetrical. The shiny seborrheic inflammation on the face was in marked contrast to the dry psoriasiform type of eruption on the extremities.

Clinical Course.—The patients were under observation over a period of several years and always showed spontaneous improvement in the summer months. The results of treatment will be recorded in a subsequent paragraph.

HISTOPATHOLOGY

Pieces of tissue were obtained from the back of the hands in Case 1 and from the psoriasiform areas in Cases 2 and 3. In addition, sections from a recent generalized case of the disease were studied. Hematoxylin and eosin, polychrome methylene blue, and Alzheimer's stains were used. The histologic appearances in all cases were similar and corresponded to those reported by other observers. The most conspicuous feature of the histology was the marked hyperkeratosis, chiefly around the mouths of the pilosebaceous follicles. The stratum corneum was greatly thickened, particularly in the older lesions and was composed of wave-like parallel laminae. The horny layer passed without interruption into the cylindrically or conically dilated mouths of the follicles and there formed onion-like concentric pearls, within which were found stumps of hairs. These colorless cornified globular pearls may occur in the epidermis doubly, apparently independently of the sebaceous or coil ducts. There were some distinctly nucleated cells in the horny layers (parakeratosis). The other layers of the epidermis showed a variable degree of hypertrophy. The rete pegs were lengthened in some sections, widened in others, and the basal layer stained more intensively than normal. Cutis changes were found in all sections and consisted of a cellular infiltrate in the papillary and subpapillary zones, chiefly about the affected follicles, and at times with a perivascular arrangement. The cells were mostly round deeply staining mononuclear fibroblastic spindle cells, and there were a few mast cells. The arrectores pilorum were markedly hypertrophic. The deeper parts of the coil and sebaceous glands showed no changes.

The conclusion I would arrive at from a study of recent papules and older ones is that the histologic changes differ only in degree. It is not possible to say whether the primary changes are in the epidermis or whether these are secondary to the inflammatory changes in the corium.

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COMMENT; SUMMARY OF PERTINENT LITERATURE

The interesting features of this group of cases are the obvious hereditary and familial tendency, the remarkable similarity of the eruption as regards distribution and certain atypical features, the mild but persistent character of the disease in the second generation, the tendency to exacerbation in the winter months and the absence of subjective symptoms. In the literature I have been able to find two reports of familial pityriasis rubra pilaris. De Beurmann, Bith and Henyer[4] report a group of four cases, two brothers, aged 23 and 25 years, and two sisters, aged 28 and 12 years. They all showed the typical pityriasic lesions on the body; a shiny uniform redness and slight desquamation of the face, hyperkeratosis of the palms with epidermal cones on the forearm, dorsal surfaces of the hands and fingers and similar lesions on the legs and feet. The nails were thick, brittle, thin at the edge and had longitudinal cracks in them. The sebaceous secretion on the face, scalp and thorax was intense, while the limbs, on the contrary, were very dry. These characteristics were present in all. In the study of the hereditary antecedents the father was found to have had for years a redness and scaliness of the face. The mother had no cutaneous affection and two other members of the family were not affected. There was a definite history of tuberculosis in the family. Recently Gaertner[5] reported a case of pityriasis rubra pilaris in a man of 29, beginning at the age of 3 years. The father had a similar affection from the fifth year to his death at 81. Gaertner would classify the disease as a congenital anomaly of cornification belonging to the so-called "universal genodermatoses" of Meirowsky, in which the "Keimplasma" is the determining factor. The familial tendency in pityriasis rubra pilaris is, however, not as marked as in such diseases as ichythyosis, porokeratosis and keratosis follicularis, but is probably more like the occasional familial tendency seen in such diseases as psoriasis.

DIFFERENTIATION FROM OTHER TYPES OF PITYRIASIS RUBRA PILARIS; RESEMBLANCE TO PSORIASIS

Pityriasis rubra pilaris, as described in the present group of cases, differs from the more severe cases originating in childhood and the

4. De Beurmann, Bith and Henyer: Ann. de dermat. et syph., 1910, p. 609.
5. Gaertner: Arch. f. Dermat. u. Syph. **129**:479, 1921.

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acute cases occuring in adults. I have had under my care three additional cases of a much more severe type, one in a child and two in adults. In the latter, the eruption at the onset consists of discrete conical papules. By close aggregation and new formation of papules, hyperkeratotic scaly patches are produced closely resembling psoriasis. The eruption rapidly becomes universal, the erythroderma and profuse scaliness suggesting an exfoliative dermatitis. After partial involution there remains a residual eruption located chiefly on the face and scalp, elbows, knees, axillae, genital region, popliteal space, sacral region, hands and feet. In these severe cases the nails show remarkable changes. The nails of both hands and feet become opaque, thickened, transversely striated and pushed upward by an enormous subungual hyperkeratosis. The distal end of the nail shows a grayish-yellow discoloration, is lifted up by a friable subungual deposit and has a tendency to curvature in a longitudinal direction, resulting in a claw-like deformity. The palmar and plantar hyperkeratosis may be so severe as to seriously interfere with the use of the limbs. The hands are often swollen and deformed with a feeling as if they were incased in a cast, as one patient expressed it. The black "plugs" on the dorsal phalanges and backs of the hands are regularly found in these cases. The preceding observations agree with the nail changes as reported by Heller,[6] Friedmann,[7] Dubreuilh and Riecke. In contrast to this is the absence of nail changes in the familial type of disease, the freedom of involvement of the trunk and the inconspicuous nature of the follicular papules on the backs of the hands. I believe we must therefore recognize that pityriasis rubra pilaris may occur as both a mild familial type and a more severe acquired form. It may be recalled in this connection that Thibièrge has already emphasized the multiformity and variability in the clinical aspects of pityriasis rubra pilaris. The resemblance of the lesions to psoriasis is worth commenting on from the standpoint of differential diagnosis. The silvery white scales covering the plaques on the elbows and knees strikingly resemble psoriasis. Careful inspection and palpation will, however, disclose acuminate papules. The absence of bleeding points on removal of the scales, and the palmar and plantar changes will be of value in the differentiation.

6. Heller: Die Krankheiten der Nägel, Berlin, 1900, p. 143.
7. Friedmann: Arch. f. Dermat. u. Syph. **135**:161, 1921.

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RELATIONSHIP TO ENDOCRINE GLANDS

The etiologic relationship of pityriasis rubra pilaris to endocrine glands is suggested by the favorable response to medication with such glandular extracts as thyroid and pituitary and the occasional association with symptoms of endocrine disturbance. Levin has demonstrated a number of cases before the Manhattan Dermatological Society which showed signs of dyspituitarism and which improved under the administration of pituitary substance. Bechet [8] mentions a male adolescent with a classical pityriasis rubra pilaris who had a typical Fröhlich syndrome characterized by excessive adiposity, deficient sweat, dry skin and dry, strawlike hair. There was slight improvement in the eruption after administering pituitary extract. The relationship to the thyroid gland is equally obscure as many cases which present no sign of a pathologic condition of the thyroid improve with the administration of thyroid extract. Levin and Smith [9] report an interesting case of pityriasis rubra pilaris with symptoms of hypothyroidism in a male adult with apparent cure by thyroid therapy. In this case they record the following symptoms: dull, stupid facial expression with minor mental changes; marked evidence of senility; sparseness of the eyebrows and absence of the outer half; relaxation of ligaments; poor muscular tone; slow pulse; extreme constipation; dry scaly, itching skin, and chilliness. The thyroid gland was not palpable. They urge the administration of thyroid extract in cases with minor symptoms of hypothyroidism as a valuable therapeutic test and even when thyroid symptoms are not present for its effect in improving the nutrition of the skin, increasing its glandular activity, stimulation of hair growth, and enhancing the desquamation of the unhealthy horny layer with reproduction of a new covering. These conditions are present in pityriasis rubra pilaris and also account for the beneficial effect of thyroid in ichthyosis and allied conditions. In my series of seven cases I was able to find definite evidence of hypothyroidism in only one, although the improvement in the cutaneous condition under thyroid administration in all was marked. In one of the unusually severe cases

8. Bechet, P. E.: The Dermatologic Symptoms of Endocrine Dysfunction, Arch. Dermat. & Syph. 4:660 (Nov.) 1921.

9. Levin and Smith: Pityriasis Rubra Pilaris: Report of a Case Cured by Thyroid, Arch. Dermat. & Syph. 3:40 (Jan.) 1921.

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of pityriasis rubra pilaris under my care at the Cook County Hospital, which rapidly became generalized under treatment with arsenic (sodium cadodylate injections) and had assumed a type resembling exfoliative dermatitis, there was remarkable improvement under treatment with thyroid extract. The desquamation and erythroderma over the trunk cleared almost entirely leaving only a few areas present on the elbows, knees and scalp. The hyperkeratotic condition of the palms and soles improved slowly under treatment. A Roentgen-ray examination of the chest in this case showed no pathologic condition, and the sella turcica was normal in outline. The basal metabolic rate was within normal limits. After taking 1 grain (0.06gm.) of thyroid three times a day for four weeks, definite symptoms of hyperthyroidism presented themselves—a marked tremor, eye symptoms and rapid pulse, necessitating discontinuation of the treatment. Thyroid extract should therefore be administered with care, and, if possible, controlled by basal metabolism tests. Regarding the possible presence of an enlarged thymus in one of my cases, I am inclined to look on this as an accidental finding. Interest in the association of the thymus gland with another dermatitis, psoriasis, has been aroused by Brock's hypothesis that there is a hypofunction of the thymus in this disease and the attempt to stimulate this by small doses of roentgen-rays.

Recently the patient mentioned in the foregoing receivd a stimulating dose of roentgen-ray over the thymus area, with continued improvement.

RELATIONSHIP TO TUBERCULOSIS

In 1901, Milian announced the theory of the tuberculous origin of pityriasis rubra pilaris, which was based on the great frequency of tuberculosis in the patients observed by him, the existence of intermediary cases between certain tuberculids and pityriasis rubra pilaris and the positive tuberculin reactions. Milian would consider the disease as a perifollicular tuberculid. Gaucher has also found that several patients treated by him for pityriasis rubra pilaris succumbed to tuberculosis. De Beurmann obtained a definite history of tuberculosis in the family studied by him. All of the members gave positive tuberculin reactions. The father had repeated attacks of bronchitis, and in one of the children the right apex was affected. Other observers have not been able to confirm these observations. In the four cases described in this report, nothing was found to indicate the presence of tuber-

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culosis. The Pirquet tests were negative and physical and roentgen-ray evidence was lacking. Even in the patient who had had the disease for twenty years there was no impairment of health. The theory of the tuberculous origin of the disease appears to rest on indefinite evidence.

THERAPEUTIC OBSERVATIONS

In the series of cases that I have had under observation the greatest amount of improvement was noted with thyroid therapy. Small doses of thyroid 1 grain three times daily (0.06 gm.) were effective in controlling the disease but failed to effect a complete cure. Possibly better results will be secured with Kendall's thyroxin. My experience with other endocrine substances was not so favorable. Arsenic, as solution of potassium arsenite, Asiatic pills and sodium cacodylate, appeared to aggravate the condition. In contradistinction may be mentioned the results of Kaposi, who cured some of his patients with heroic doses of arsenic, and Heidingsfeld who managed three cases successfully by the administration of intestinal antiseptics, a carefully regulated diet, the external application of tar and the hypodermic administration of arsenic in the form of atoxyl, or cacodylic acid. Pilocarpin, a remedy formerly much used, I have had no experience with. Diet has not influenced the course of the disease. Locally, I have found the free use of baths followed by some mild emollient, such as benzoinated lard or lanolin, better then stronger keratolytic or reducing agents. The careful use of the roentgen ray appears to aid in the involution of the lesions. The disease in my experience improves up to a certain point, but becomes refractory to further roentgenization.

CONCLUSIONS

1. Pityriasis rubra pilaris may occur as a hereditary, familial disease.
2. The familial type of disease represents a mild persistent dermatosis beginning in early life and presenting atypical features resembling psoriasis.
3. The disease is occasionally associated with evidences of endocrine gland disturbance.
4. There is no evidence of a relationship to tuberculosis.
5. Thyroid extract is the most valuable therapeutic agent in controlling the disease.

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ABSTRACT OF DISCUSSION

Dr. Richard L. Sutton, Kansas City, Mo.: The point Dr. Zeisler brought out regarding an occasional familial tendency in this disease should be emphasized. In chronic skin diseases of doubtful etiology, one should be careful in giving advice regarding the probable freedom from inheritance of the offspring. In this instance, the patient undoubtedly blamed the physician who had told him that there was no danger of his children contracting or inheriting the disease. A few years ago, I was consulted by a patient with a large and unsightly birthmark, who wanted to know if it would be safe for him to marry and beget children. I told him that the condition sometimes was an inherited one. The first (and thus far only) baby had a disfiguring birthmark, similar to the one carried by the father.

Dr. Harold N. Cole, Cleveland: I saw one of the patients Dr. Zeisler referred to when she was in Cleveland, and she had a characteristic case of pityriasis rubra pilaris.

Dr. David Lieberthal, Chicago: I do not believe Dr. Zeisler is to be criticized for not advising against marriage. So far as I know, the first patient was married twenty years or more ago, and at that time Dr. Zeisler was not in practice and none of us had all the information we have gained since that time in regard to this and many other diseases.

Dr. William Allen Pusey, Chicago: These facts were not known to many of us before. I am glad to learn that the affection is familial, and the opinion of Drs. Sutton and Lieberthal makes little difference.

Dr. Erwin P. Zeisler, Chicago, closing: I believe my paper emphasizes the point that care should be exercised in permitting patients with chronic dermatoses to have children. Even such disorders as psoriasis are occasionally hereditary, and patients should be informed of this fact.

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LUPUS ERYTHEMATOSUS ACUTUS DISSEMINATUS HEMORRHAGICUS

REPORT OF A CASE

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LOS ANGELES

The following case is reported, both because of the extreme rarity of the condition, and because of the several interesting clinical features of the case. The case was referred to me by Dr. D. Edelman of this city.

REPORT OF CASE

Aug. 5, 1920, Mrs. C. M., aged 31, mother of two children, consulted her family physician about two red patches on the forehead and on the chest. She had noticed the patches for the first time two weeks before. They caused burning and itching and grew steadily bigger. She had also been complaining of weakness, severe headaches and of general ill feeling for the last six months. The family physician had found a large amount of albumin in the urine and had prescribed a general and dietetic regimen. He referred the patient for a dermatologic diagnosis.

Skin Findings.—The examination revealed a very sharply defined, acutely inflamed area, occupying the nasal bridge, descending symmetrically on both cheeks and presenting a typical bat-wing shape. The patches were not bright, angry red, but rather deep red and livid. They showed a very slight infiltration, with a greater turgescence at the border and a perceptible flattening of the central parts, which were paler and gave a suggestion of mild sclerosis or atrophy. The surface of the patches was rather greasy and smooth, showing fine dirty white tightly adherent branlike scales. An irregularly shaped square patch, about 2 by 3 inches (5 by 7.5 cm.), of the same clinical characteristics was found on the upper third of the sternum.

Physical Examination.—Examination revealed: head and neck: no exophthalmos, thyroid palpable but not enlarged, oral cavity presenting no abnormalities. Chest: heart of normal size, shape and position, heart tones clear and distinct. Lungs: definite right apical retraction and fibrosis, dulness to flatness,

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supraclavicular to fourth interspace; breath sounds exaggerated, bronchial blow with harsh inspiration; left base lung excursion restricted with a reduction of vesicular breathing; inspiration productive of cloudburst of crackling. Impression of the chest condition: chronic fibroid tuberculosis (quiescent), and left basal adhesive pleuritis. The abdomen was rotund; there was no distention, and fat was retained; no masses were palpable, and there were no tender areas on deep palpation; liver, kidneys, spleen were not palpable. Superficial and deep reflexes were present, but there was no Argyll Robertson pupil, nor ataxia.

Laboratory Findings.—Examination of the blood revealed that bleeding time was normal and coagulating time greatly prolonged (Howell's method). Hemoglobin was 63 per cent., the red blood cells numbered 3,200,000, the color index was 0.95; the leukocytes numbered 5,200. Differential leukocyte count revealed: polymorphonuclears, 136 (68 per cent.); lymphocytes, 50 (25 per cent.); large mononuclears, 11 (5.5 per cent.); transitionals, 3 (1.5 per cent.); total, 200 (100 per cent.). The red blood cells were normal in size, regular in shape and took the stain evenly. No nucleated red blood cells or blood parasites were seen, and no abnormal leukocytes. Platelets diminished in numbers. The blood culture was sterile; the Wassermann reaction, one plus. Examination of the urine revealed a trace of albumin. Microscopic examination of centrifugalized sediment revealed numerous red blood cells, pus cells and numerous bacteria. No casts were found.

Diagnosis.—The morphology and localization of the lesions on the face were so typical of lupus erythematosus that no other diagnosis was seriously considered. There were three unusual features: (1) an acute development; (2) the presence of constitutional symptoms, and (3) the presence of a clinically identical patch in the region of manubrium sterni—a distinctly seborrheic location. For this reason the possibility of an atypical seborrheic dermatitis was entertained temporarily in spite of the absence of seborrhea on the scalp, except a slight dandruff. Two per cent. salicylic acid in Lassar's paste was given.

Clinical Course.—Two weeks later, I was again called to see the patient at her home. She was confined to bed, complaining of weakness and feverish spells at night. There was a considerable extension of the lesions of the face, forming large symmetrical butterfly-shaped areas of the classic type of lupus erythematosus, extending down on the cheeks and also on the forehead. Beyond the sharply defined borders of the main areas appeared numerous small, discrete, though not nearly so sharply marginated, maculopapular lesions, ranging in size from that of a hemp seed to that of a coffee bean. These lesions were dusky red and perfectly smooth, suggesting papular lesions of erythema multiforme type. A few days later, multiple lesions of the same type appeared on the right arm and on the following days successively on both elbows, gluteal regions, legs and other parts of the body. A few similar maculopapular lesions could be seen on the hard palate. The patient complained persistently of a burning sensation in the large patches on the face and sternum, but the disseminated lesions on the limbs and trunk did not cause any discomfort.

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At this time, the large patches on the forehead, cheeks and sternum had undergone a most peculiar change. They had suddenly developed a diffuse oozing of a hemorrhagic character, not merely a blood serum, but what seemed to be pure blood. In fact, it was, clinically, a striking picture of a cutaneous hemorrhage spontaneously developed. Blood was oozing slowly, forming heavy hemorrhagic crusts. Bleeding could not be stopped by pressure, but it was easily controlled by 1 : 1,000 epinephrin ointment. Gradually, the patches on the face lost their originally sharply marginated borders, fused with disseminated maculopapular lesions and formed rather diffuse areas of erysipeloid hue, covering practically the whole face. Similar changes took place in the sternal patch.

The rash, as a whole, had attained its maximum; it remained stationary for a week, and gradually began to recede. During this time, the patient had irregular and intermittent elevations of temperature up to 102 F., which also gradually went down to normal.

The treatment consisted in the administration of quinin hydrochlorid, 5 grain capsules, four times a day, and 5 grain capsules of calcium lactate, four times a day, given at alternate hours.

By September 30, about two months after the appearance of the first patches, all skin lesions had cleared up completely. The patient improved sufficiently to be up and about, and I withdrew from the case, leaving the patient in charge of the family physician.

Subsequent History.—The attending physician reported that the subsequent course was unexpectedly rapid and dramatic. In spite of the apparent improvement, the patient did not recover completely. There were, as before, indefinite complaints with no other clinical findings but persistent albuminuria, red blood cells, pus cells and hyaline, granular and blood casts in the urine. At one time, small purpuric spots appeared scattered over the body. December 17, the patient became unconscious and died, with a typical picture of uremia. At the partial necropsy examination made by Dr. A. Zeiler, no active tuberculous lesions were found, but a well expressed pyonephrosis.

REVIEW OF THE LITERATURE

As the foregoing clinical report shows, this was a case of acute hemorrhagic disseminated type of lupus erythematosus with a fatal termination—a case in which no active tuberculous lesions were found and in which the only source of focal infection responsible for the whole symptomatology proved to be pyonephrosis.

Cases of this type are extremely rare. One of the earliest cases of lupus erythematosus disseminatus was reported by Hardaway,[1] in 1889. The patient, aged 26, having discoid patches of lupus erythematosus

1. Hardaway: J. Cutan. Dis. **7**:447, 1889.

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on the face for several months, developed bullae, after some irritating local medication fever, with hemorrhagic crusts, enlarged lymphatic glands, coma and acute tuberculous pneumonia, resulting in death. Fordyce,[2] in 1896, reported a case of a woman, aged 25, who, after having discoid patches on the face for many months, developed multiple similar patches, disseminated on arms and hands, at the beginning of pregnancy. At the end of pregnancy, the eruption cleared up, leaving behind atrophic marks.

Pernet,[3] in 1908, quoted a series of ten cases of lupus erythematosus acutus disseminatus reported up to date: among these were one case of his own, three reported by Kaposi, one by Boeck, one by Koch, two by Jadassohn, one by Short and one by Heath. Strangely, he does not mention the cases of Hardaway and Fordyce. Gray,[4] in 1914, reported a case of a young woman suffering with pneumonia who developed patches of lupus erythematosus with hemorrhagic bullae on the face and hands. After the resolution of pneumonia, the rash cleared up also, but reappeared later as ordinary discoid patches.

Ravogli,[5] in 1915, reported a case of lupus erythematosus of discoid type in which, after injections of 0.01 mg. of tuberculin, a disseminated form of lupus erythematosus developed with fever and early death from miliary general tuberculosis.

Barber,[6] in 1915, reported a case in which, after recurrent attacks of discoid patches for several years, the lesions spread acutely on the face, body and limbs, associated with elevations of temperature, up to 104 F. A pure culture of *Streptococcus longus* was obtained from the intestines. After the improvement brought about by sour milk treatment, no streptococci were found in the feces, only *Bacillus coli* and allied bacilli being present. Ijiri,[7] in Japan, reported, in 1915, three cases of acute lupus erythematosus disseminatus. Ehrman,[8] in 1917, reported the case of a soldier who, after an injection of infected tuberculin,

2. Fordyce: J. Cutan. Dis. **14**:89, 1896.
3. Pernet: Etude Clinique, Paris, 1908, p. 135.
4. Gray: Brit. J. Dermat. **26**:356, 1914.
5. Ravogli: J. Cutan. Dis. **33**:266, 1915.
6. Barber: Brit. J. Dermat. **27**:365, 1915.
7. Ijiri: Ztschr. f. Dermat. **15**: (July) 1915.
8. Ehrman: Wien. klin. Wchnschr. **30**:669, 1917.

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developed disseminated acute erysipelas-like lesions on the face, trunk and limbs. The lesions developed later into chronic discoid patches.

Brown,[9] in 1917, reported the case of a boy, aged 11, in whom patches of lupus erythematosus appeared on the ears. Four weeks later, he developed fever and vomiting; the patches disseminated on the nose, cheeks, fingers and toes, and the gums bled. As the rash faded, the patient developed pneumonia, and died four days later. There was no tuberculosis in the family, and the tonsils had been removed three years before.

Several cases were reported in 1920. Highman[10] reported the case of a woman, aged 51, who had discoid patches of five weeks' duration. She developed erysipeloid areas on the face and hands, with elevation of temperature and prostration. The lesions were proved histologically to be lupus erythematosus.

An interesting case was reported by Low and Rutherford.[11] The patient had discoid patches on the face for years; she also had pyorrhea and subacute nephritis. The skin lesions cleared up after the extraction of teeth and vaccine treatment, but recurred after each of four attacks of bronchitis which the patient had in four and a half years, with complete disappearance of the eruption between the attacks. In the sputum were found streptococcus and staphylococcus. The patient died from intercurrent diphtheria. At necropsy, no active tuberculosis was found, but there were extensive chronic lesions in the lungs. Streptococcus was cultured from the blood.

Graham Little[12] reported a case in which discoid patches of seven months' duration on the nose spread all over the body, with elevation of temperature. Tuberculous glands were present. Whitfield[13] reported a case of acute lupus erythematosus with a fatal termination. The necropsy findings were negative. Sequeira[14] reported the case of a woman, aged 37, in which discoid patches appeared on the nose, covered its whole surface and then spread to other parts of the body, fingers

9. Brown: New York M. J. **106**:931 (Nov. 17) 1917.

10. Highman, W. G.: Lupus Erythematosus Disseminatus, Tr. New York Dermat. Soc., Arch. Dermat. & Syph. **1**:227, (Feb.) 1920.

11. Low and Rutherford: Brit. J. Dermat. **32**:326 (Nov.) 1920

12. Graham Little: Brit. J. Dermat. **32**:272, 1920.

13. Whitfield: Brit. J. Dermat. **32**:272, 1920.

14. Sequeira: Proc. Roy. Soc. Med. **13**:27 (Feb.) 1920.

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and toes. On the hands were purpuric and hemorrhagic lesions; on the right calf appeared bullous lesions. The temperature was normal. There was no albuminuria. He cited another acute case, with a temperature of 103 to 105 F. Ormsby[15] cited two fatal cases of lupus erythematosus acutus (unpublished) with the lesions of erythema multiforme type scattered on the body. McLeod[16] recorded a fatal case of acute lupus erythematosus with nephritis. The eruption cleared up as the nephritis grew worse.

The analysis of the literature on the subject leaves an impression that many writers did not sufficiently differentiate between the acute and disseminated types of lupus erythematosus. A case may be disseminated but not necessarily acute. Many cases of disseminated lupus erythematosus run a chronic course throughout. They may develop from a discoid type or be disseminated from the start. They may also start as an acute disseminated type and run into a chronic discoid type. Such cases should not be termed acute disseminated lupus erythematosus. Only cases which start acutely, assume a disseminated form and run acutely throughout can be regarded as a pure type of acute disseminated lupus erythematosus.

From this point of view, the cases reported by Hardaway, Fordyce, Ravogli, Barber, Ehrman, Low and Rutherford, and Graham Little can hardly be considered as pure types of acute disseminated lupus erythematosus, but rather as a chronic disseminated type with an acute exacerbation. On the other hand, cases reported by Highman, Gray, Brown, Whitfield and Sequeira answer all qualifications of acute disseminated lupus erythematosus. The present case is the sixth of this class. In the remainder of the series of sixteen cases reported, the available data are not sufficiently detailed to determine their type.

As to the other salient features, out of twenty-seven reported cases of lupus disseminatus, seven terminated fatally, those reported by Hardaway, Short, Brown, Low and Rutherford, Whitfield, Ravogli and McLeod. The present case is the eighth fatal case.

As to the hemorrhagic lesions, they were present only in four cases of the series, those reported by Kaposi, Hardaway, Gray and Sequeira. The present case is the fifth.

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15. Ormsby: Diseases of the Skin, Philadelphia, Lea & Febiger, 1921, p.698.
16. McLeod: Brit. J. Dermat. **20**:236, 1908.

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PATHOGENESIS

The pathogenesis of lupus erythematosus is notoriously a controversial issue. It seems that the study of acute forms of lupus erythematosus would hold out a better promise to establish a definite pathogenesis. This has not been the case. The analysis of twenty-seven case reports cited in the foregoing shows a diversified pathogenesis.

One point has been settled; namely, that tuberculosis, regarded for a long time the sole or the main cause of lupus erythematosus, can be definitely excluded in many cases. It was present in the cases of Hardaway, Ehrman, Ravogli and Graham Little. On the other hand, in two fatal cases of acute lupus erythematosus cited by Torok, no tuberculosis was found at necropsy. In the cases of Cranston Low, Whitfield and Brown also, the necropsy findings were negative. Of twelve cases of disseminated lupus erythematosus reported by Jadassohn, only two showed active tuberculosis, and in two others it was inactive. Barber, in two of his cases, found focal streptococcic infection in the intestines in one and in the tonsils in the other. In Fordyce's cases, the outbreak was caused by pregnancy. Pneumonia was a factor in the cases of Shamberg, Gray and Brown.

The present case shows one pathogenic factor only—a pyogenic nephritis. It is of interest to note that nephritis in this case is not secondary to some local or general infection or toxemia, but is a primary lesion, responsible both for the skin lesions and for the fatal termination, and present in the clinical picture from the very start to the finish.

The theory of a multiple and diverse pathogenesis of lupus erythematosus has been advanced and accepted by several observers, among them Brooks, Jadassohn, Hartzell and Pusey. The study of the reported cases and of the present case strongly substantiates this view.

MORPHOLOGY

The morphology of the present case was extremely interesting. The initial patches on the forehead and the sternum were of the classic type of lupus erythematosus. The subsequent lesions which developed, when dissemination took place, were of maculopapular type, strongly suggesting generalized erythema multiforme.

For a while, the eruptive areas on the face strongly suggested an erysipeloid appearance in the color of the general configuration, the only difference being that the involved area did not show one solid

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uninterrupted surface, but a confluent one, of many small ill defined patches separated by small interspaces of normal skin. The papular lesions on the trunk and limbs were characteristic of the fugaceous small papular type of toxic exudative erythema multiforme.

It is of interest to note that the skin lesions cleared up completely with the subsidence of the acute attack and that no other skin lesions, with the exception of small scattered purpuric macules, developed later when the case entered its grave and ultimate stage. Apparently, the skin lesions of lupus erythematosus in the present case were merely a temporary and incidental feature of the whole clinical picture of pyogenic toxemia.

The most striking morphologic feature of the case was a hemorrhagic exudate that developed on the initial patches on the face and the sternum at the acme of the acute stage. The exudate was diffuse, capillary, purely hemorrhagic, of bright arterial character. It was, apparently, due to intense vascular engorgement and was associated with a marked subjective feeling of burning. It did not yield to pressure but was easily controlled by epinephrin ointment. It presented a perfect picture of diffuse cutaneous hemorrhage. Hemorrhagic lesions in the form of vesicles, bullae and purpuric macules were recorded by Kaposi, Hardaway and Gray and, as purpuric and discrete hemorrhagic lesions, by Sequeira, but I did not find any references to diffuse hemorrhagic lesions, as in the present case.

LUPUS ERYTHEMATOSUS VERSUS ERYTHEMA MULTIFORME

In correlating and interpreting the fact that the initial patches are of typical discoid type of lupus erythematosus, and that subsequent disseminated lesions strongly suggest papular erythema multiforme type, two modes of explanation present themselves as the most plausible. The first is that, in certain cases reported as lupus erythematosus acutus disseminatus, the two conditions of lupus erythematosus and of erythema multiforme, induced by different pathogenic factors, were two independent clinical entities, merely coexisting in one person, without any pathogenetic relationship and only apparently merging into one clinical picture. In other words, we may assume that erythema multiforme has been superimposed by an intercurrent infection or toxemia on lupus erythematosus, and that in such cases erythema multiforme may overshadow, disguise and even modify the original discoid patches of

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lupus erythematosus. This assumption is particularly plausible in cases in which, after the termination of intercurrent infection or toxemia, the lesions return to the original discoid type.

The other explanation of the morphologic transformation observed in these cases raises an important issue as to whether lupus erythematosus is a definite clinical entity or merely a certain clinical type of skin reaction potential of multiple etiology. This interpretation would closely link lupus erythematosus with erythema multiforme. As mentioned before, this point of view has already been voiced by Fordyce, Hartzell, Pusey and other writers, who point out the existence of borderline types between lupus erythematosus and erythema multiforme. The present case admits only the second interpretation. We cannot assume in this case an intercurrent infection or toxemia that has superimposed erythema multiforme on lupus erythematosus, since we have here only one pathogenic factor—pyonephritis responsible for all the symptoms and skin manifestations in the case.

What factor determines this morphologic transformation, and why disseminated lesions do not have the slightest clinical resemblance to the discoid patches, can be suggested only in a conjectural form. Possibly, the very intensity and rapidity of the pathologic process prevents lesions from developing into ordinary discoid type.

SUMMARY

1. The female sex is preponderant in cases of lupus erythematosus acutus.

2. Lupus erythematosus acutus may be due to focal infection from the kidneys.

3. Lupus erythematosus acutus may present lesions of diffuse cutaneous hemorrhages.

4. Skin lesions in lupus erythematosus acutus may clear up in spite of the unfavorable continuation of the systemic condition.

5. Acute lupus erythematosus is a herald of focal infection and calls for a thorough search for it.

6. Lupus erythematosus acutus is in close pathogenetic relationship with erythema multiforme.

7. A stricter differentiation should be exercised in reporting cases as lupus erythematosus acutus disseminatus. A case may be disseminated

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without being acute. Only cases which start acutely and run as such throughout should be termed lupus erythematosus acutus disseminatus.

DISCUSSION

Dr. W. H. Goeckerman, Rochester, Minn: This case strikes at fundamental pathology responsible for dermatoses. Within the last few years I have seen two cases of acute disseminated lupus erythematosus come to necropsy. Both had been under the observation of a dermatologist and clinician for several months, and it was impossible to find any evidence of tuberculosis. An exploratory abdominal section was made because of the indefinite abdominal symptoms present, and even then we were unable to find any evidence of abdominal tuberculosis; but at the postmortem examination both cases showed involved abdominal glands, and the organism was demonstrated definitely in smears. I was impressed with the fact that we could not clinically determine the presence of tuberculosis when only the abdominal glands were involved. Gennerich, within the last year, reported a case in which he found definite gland pathology, but he was not willing to say that it was tuberculosis. I kept these observations in mind and determined that on the first occasion I would attempt to treat a case along the line we were treating Hodgkin's disease, with deep roentgen-ray therapy. About six or eight months ago a case was presented that somewhat resembled that of Dr. Scholtz'. The patient had marked lesions in the mouth; his hair had practically all dropped out. A week after the first treatment he had decidedly improved. A few weeks later the symptoms had all disappeared, the hair had grown in and he had gained in weight. I heard from him last week, and he said that he was doing the chores on his brother's farm, and none of the cutaneous lesions had reappeared. As to whether we learned anything about the etiology of lupus erythematosus in this case, I would not venture to say; but I wish to call attention to the desirability of repeating this form of treatment in other appropriate cases.

Dr. Everett S. Lain, Oklahoma City: I am especially pleased to hear another confirmation of an opinion I have held since the work of Rosenow on focal infections, namely, that lupus erythematosus is also a result of focal infection. My attention was first directed to this relation by seeing a patient with both herpes zoster and lupus erythematosus. I have many times seen clinical evidence of this apparent relationship. I am trusting that some one may prove or disprove this theory. It is my opinion that lupus erythematosus is merely a skin reaction to a toxin, probably having various foci of pathogenesis.

Dr. William T. Corlett, Cleveland: The etiology of lupus erythematosus has been for many years the subject of controversy, and the prevailing opinion as to its causation has shifted from time to time, the latest being that it is due to the presence of one or more foci of tuberculosis. Before Dr. Stokes published his interesting and complete article on his findings in a number of cases I was inclined to the opinion, my clinical experience at least had led me to so believe, that lupus erythematosus was not associated with tuberculosis,

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because in the cases I had seen there had been no evidence, so far as I was able to determine, of an infection of tuberculosis—that is, generalized or marked tuberculosis. Dr. Stokes, however, led me to believe that there might be insignificant foci in various parts of the body that had been overlooked by the ordinary means of examination, and since reading his article I have sought more carefully for evidence of tuberculosis whenever lupus erythematosus presented itself. I have never been convinced, however, that it was the only cause of the disease, and I am glad to hear another view, a little broader it may be, set forth in regard to its etiology. I still feel, however, that the last word has not yet been said as to the etiology of lupus erythematosus.

Dr. Marcus Haase, Memphis, Tenn.: I recall the case of an elderly woman who had three attacks of acute disseminate lupus erythematosus. I saw her in the last attack and she had none of the fixed type of lesions. From the information I received from her physician, a general practitioner, I learned that the attacks had disappeared within from three to five weeks of their onset, and that they came on suddenly. When I saw her, she had lesions on the face, over the upper arms and on the chest. The family physician said that the lesions she had during this third attack could not be differentiated from those he had seen in the two previous attacks. This woman was suffering from pyelonephrosis at that time and was under the care of an internist. What I wish to bring out is that if her two previous attacks were similar to the one she had at that time, then this case could not have been mistaken for a case of erythema multiforme, and while I am not positive of my diagnosis of acute lupus erythematosus, at the time I saw her it was my opinion that she had that disease.

Dr. William Frick, Kansas City, Mo.: With all our studies of lupus erythematosus we have not been able to find any direct connection between that disease and tuberculosis. It seems to me that the preponderance of opinion would be that it is a toxic condition, and I do not see why we should not have a toxic condition producing lupus erythematosus in a tuberculous case, whether of the lungs or elsewhere. This paper seems to confirm the belief that lupus erythematosus is due to a toxic condition and may be due to conditions other than tuberculosis, and at the same time it may develop in a patient with tuberculosis. In other words, it may be due to various causes.

Dr. Richard L. Sutton, Kansas City, Mo.: At present, we can divide these cases into two distinct types, the acute and the chronic. The acute is almost always, if not invariably, due to tuberculosis, and the chronic is a symptomatic manifestation of any one of a number of factors. For many years, I have shared the opinion of Drs. Chipman, Lain, Stokes, Highman and others, that focal infection plays an important part in the causation of many of the chronic cases, and I do not believe that any patients with chronic lupus erythematosus should undergo a course of treatment until this possibility has been thoroughly investigated. Hartzell has recently reported a case in which the removal of an infected tooth was followed by a spectacular disappearance of the cutaneous

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lesions, and many English observers likewise have called attention to focal infection as a probable etiologic factor in the chronic type of the disease.

Dr. Moses Scholtz: To me the point of interest was the morphologic relationship between lupus erythematosus and erythema multiforme. Here we had the typical lesions of lupus erythematosus superseded and modified by lesions of erythema multiforme. The question is, Were these both due to the same etiologic factor? In my opinion cases like this suggest that lupus erythematosus is not an independent clinical entity but merely a certain type of skin reaction; and I was glad to hear at least one opinion to substantiate this view.

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PHYSICAL PRINCIPLES UNDERLYING THE DEVELOPMENT OF HIGH VOLTAGE ROENTGEN-RAY APPARATUS

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SCHENECTADY, N. Y.

Until recently, most roentgenotherapy was practiced with voltages up to approximately 100,000 applied to the roentgen-ray tube. The roentgen rays generated at these voltages produced definite biologic reactions at or near the surface of the body. Because of their comparatively low penetrating power, however, these rays were rapidly absorbed by the tissues, and it was difficult to deliver any effective amount to a point much below the surface without injury to the overlying tissue.

Figure 1 gives a visual picture of absorption of roentgen rays as they pass through matter. It shows a cube of lead glass which was placed beneath a half inch opening in a lead diaphragm and exposed for several hours to the rays from a tube operating with four milliamperes at 200,000 volts (peak). This glass becomes brown under the influence of roentgen rays, and the intensity of the coloration indicates the intensity of the roentgen-ray beam at different depths below the surface of the glass. It will be noticed that the color is very dark at the surface and gradually becomes lighter as the depth increases. This illustrates the physical problem involved in deep roentgenotherapy, which, as I have said before, is one of getting sufficient roentgen-ray intensity at a point much beneath the surface of the body.

In the past, the use of multiple ports of entry and of cross-firing was resorted to in an endeavor to increase the intensity beneath the surface. Results obtained by this method are illustrated by Figure 2. In this case, a similar glass cube was exposed from four sides in succession and an area will be seen in the center of the cube where the combined roentgen-ray beams have produced an effect nearly equal to that produced by any one beam at the surface.

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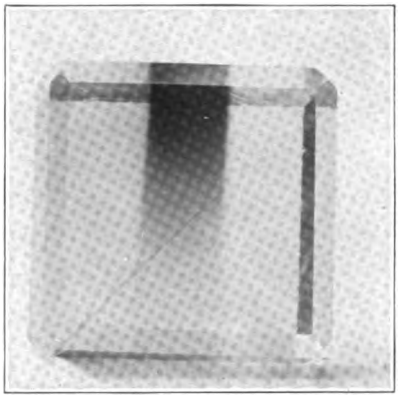

Fig. 1.—Absorption of roentgen rays in matter shown by color produced in cube of lead glass.

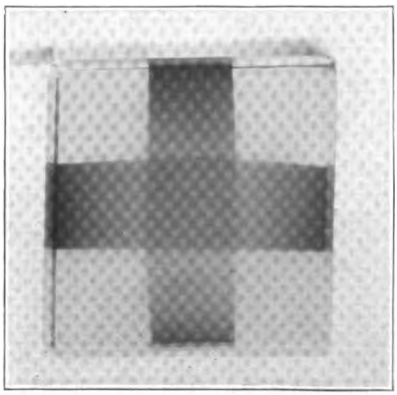

Fig. 2.—Cross-fire technic illustrated by color produced by roentgen rays in lead glass cube.

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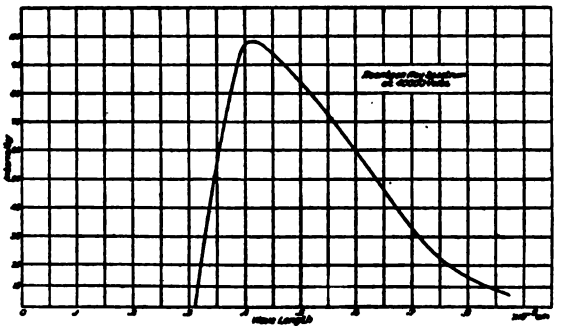

Fig. 3.—Spectrum of roentgen-ray beam from tube operating at 40,000 volts.

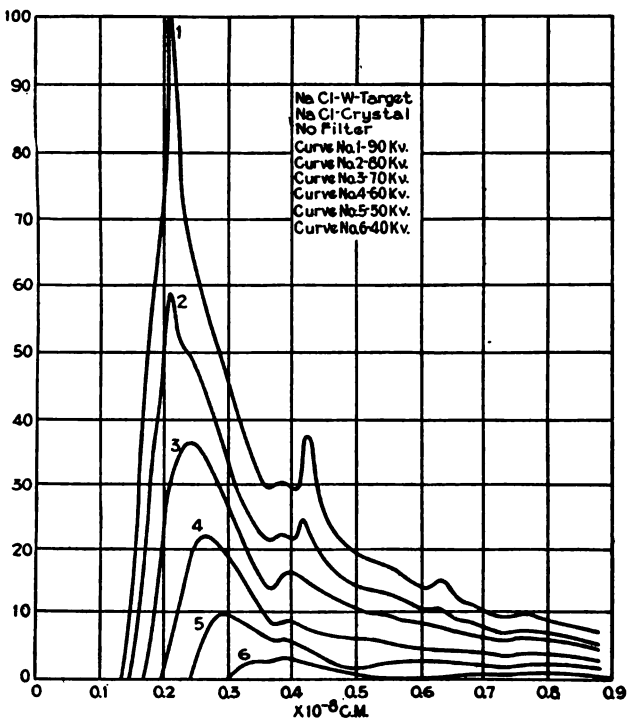

Fig. 4.—Roentgen-ray spectra from tubes operating at from 40,000 to 90,000 volts.

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During the last few years, the tendency has been toward the use of higher voltages, in an attempt to increase the ratio of depth to surface dose. It is the physical principles underlying this method of attack that I am to review in this paper. Tubes to operate at the higher voltage and apparatus to produce this voltage had to be developed, and the experimental work involved in this development was undertaken only after careful physical measurements had shown that a greater intensity at a depth could be produced by the use of higher voltage.

That the results of these measurements may be understood more clearly, let us first consider the beam of roentgen rays coming from any roentgen-ray tube. By means of a Bragg spectrometer and ionization chamber, we may analyze this beam, and plot the spectrum, just as we would analyze the beam of light from an incandescent lamp. In doing so, we find that it is a composite beam made up of waves of varying lengths. Figure 3 presents a spectrum of the roentgen-ray beam operating at 40,000 volts,[1] and we find that the wave lengths vary from 0.3 Å to 0.8 Å,[2] with a maximum of intensity at about 0.4 Å. We know that the shorter the wave length, the more penetrating power the roentgen-ray wave has, so that we are interested in anything that will give us a shorter wave length and a greater intensity of this shorter wave length.

Figure 4 shows the effect on the wave length and intensity of increasing the potential applied to the roentgen-ray tube. At 40,000 volts, the shortest wave length is about 0.3 Å, and this decreases to about 0.1 Å at 90,000 volts. At the same time, the intensity of the waves of shorter length has tremendously increased. There are still a lot of long wave lengths present, however. The same thing holds true as we go to still higher voltages, as is shown in Figure 5,[3] which gives the spectrum at 165,000 volts. Here the shortest wave length is 0.075 Å. The wave length of the gamma rays from Ra-C is approximately 0.004 Å. According to the work of Ellis in England, it would require a voltage of 3,000,000 on the tube to produce roentgen rays of this short wave length. It is evident from these measurements that increasing

1. Hull: Am. J. Roentgenol., 1915.

2. The Angström unit, 10^{-8} or $1/100{,}000{,}000$ cm. is the standard unit for expressing wave length.

3. Duane: Am. J. Roentgenol., March, 1922, p. 169.

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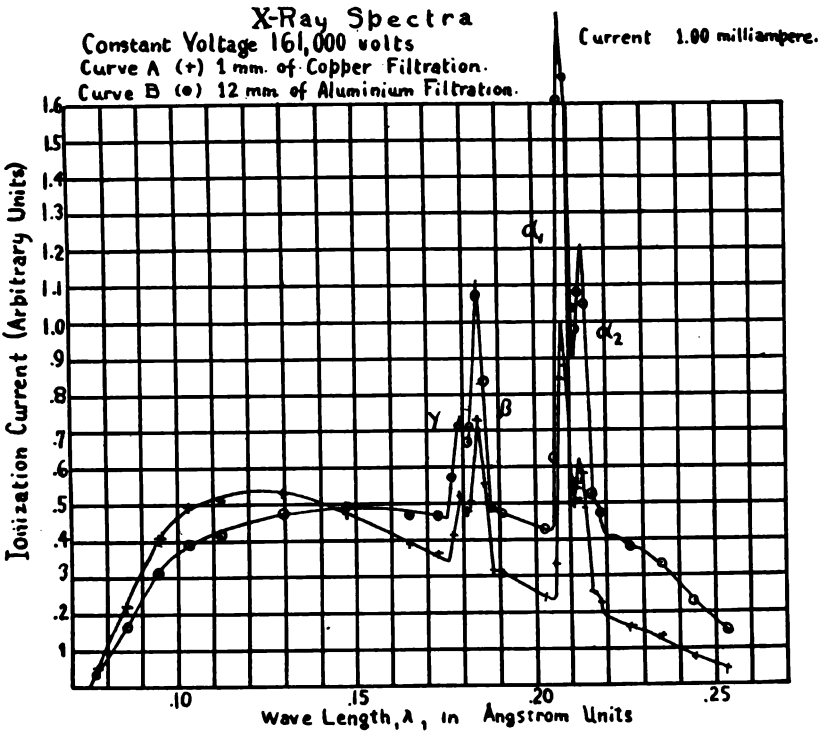

Fig. 5.—Roentgen-ray spectrum from tube operating at 165,000 volts.

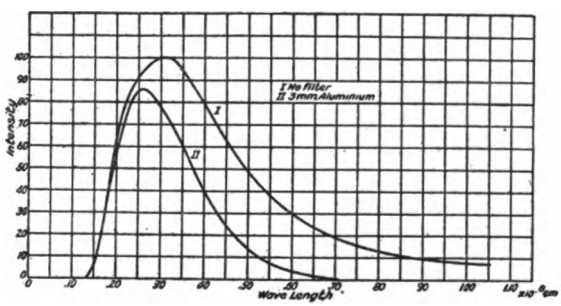

Fig. 6.—Roentgen-ray spectra at 70,000 volts with and without aluminum filter.

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the potential applied to the tube results in the production of a greater quantity of more penetrating rays.

For the purpose of cutting off the longer or less penetrating rays, it is customary to pass the roentgen-ray beam through some filter, a sheet of aluminum or copper, before it reaches the body. The effect of such a filter is shown in Figure 6,[4] in which the upper curve shows the spectrum at 70,000 volts without any filter and the lower curve the spectrum with a 3 mm. aluminum filter. It can be seen that the aluminum has reduced the intensity of the soft radiation (long wave lengths) much more than that of the penetrating rays, but there is still a considerable amount of soft radiation left. This could, of course, be considerably reduced by the use of a great thickness of aluminum or a sufficient thickness of some denser material, such as copper, but not without cutting down the intensity of the useful penetrating rays to a small fraction of its original value. But we have already noted the effect of increasing the potential applied to the tube. Therefore, we are able to combine the two, higher voltage and greater filtration, to obtain a sufficient intensity of the more penetrating rays. This is shown in Figure 7,[5] where we have plotted the intensities through different thicknesses of copper filters at various voltages of from 175,000 to 298,000. It will be noticed that for any voltage the intensity falls off rapidly with increasing thickness of filter, and that for any one filter thickness, for example 1 mm., the intensity increases rapidly with the voltage. When high intensity of penetrating radiation is desired, there is a strong argument in favor of the use of high voltage with sufficient filtration.

So far we have been considering the roentgen-ray beam before it reaches the body of the patient. In deep roentgenotherapy, what we are interested in is the nature of the beam after it has passed through a certain amount of tissue on its way to the diseased area. To determine the physical characteristics of the beam within the body, we are accustomed to choose some material, such as water, which has about the same absorbing power as the body, and measure at some desired depth in the water, by means of the ionization chamber, the roentgen-ray intensity with tubes operated at various voltages and with filters of various

4. Hull: Am. J. Roentgenol., 1915.

5. Coolidge and Kearsley, Jr.: Am. J. Roentgenol., February, 1922, p. 98.

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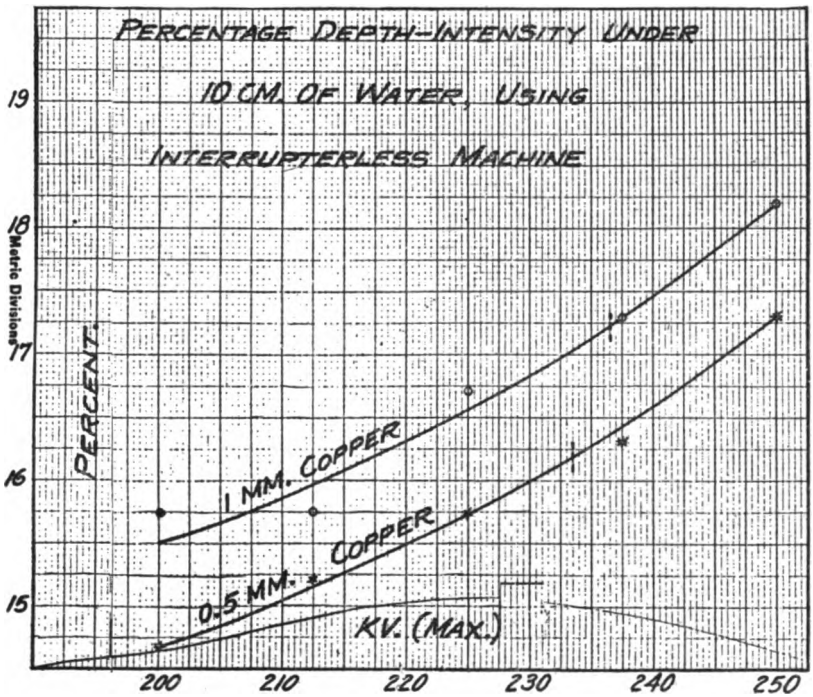

Fig. 8.—Percentage depth dose beneath 10 cm. of water.

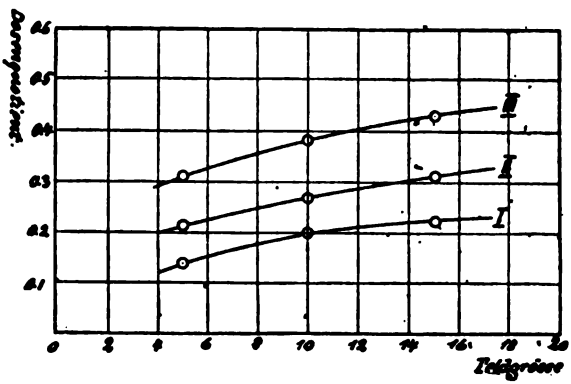

Fig. 9.—Effect of size of port of entry on percentage depth dose.

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thicknesses. The results of such measurements are given in Figure 8.[6] Here we have plotted the percentage intensity beneath 10 cm. of water with the roentgen-ray tube operated at voltages of from 200,000 to 250,000, and with the roentgen rays filtered through 0.5 and 1.0 mm. of copper. With one-half millimeter of copper as a filter, the roentgen-ray intensity beneath 10 cm. of water is 14.75 per cent. of what it is at the surface of the water when 200,000 volts are applied to the tube, while it is 17.25 per cent. if 250,000 volts are employed. A similar increase is shown with 1 mm. of copper filter. The curves indicate clearly that, up to 250,000 volts at least, the percentage depth intensity increases with increased voltage and that it is greater the thicker the filter.

A third factor enters into the question of percentage depth dose; namely, that of distance from the focal spot to the surface of the body. In any particular case, the distance from the surface to a point beneath at which the roentgen rays are to be delivered is a constant, and the ratio of this distance to the total distance from the focal spot becomes less as the latter distance is increased. At low voltages, it was impossible to greatly increase the focal spot skin distance because the roengen-ray intensity decreases inversely in proportion to the square of the distance; that is, the greater the distance, the less the intensity. We have seen, however, that this decrease in intensity may be compensated for by increased potential applied to the tube, and increased filtration of the roentgen-ray beam.

As a fourth factor, we have to consider the size of port of entry in regard to its effect on the percentage depth dose. The results of measurements made to determine the effect of varying this factor are given in Figure 9.[7] These curves show the percentage depth dose beneath 10 cm. of water for rays filtered through 3 mm. of aluminum, 10 mm. of aluminum, and 1 mm. of copper for three ports of entry, 5 by 5 cm., 10 by 10 cm., and 15 by 15 cm. It is evident from these curves that, within these limits, the percentage depth dose increases as the size of port of entry is increased. The explanation of this lies in the fact that roentgen rays in passing through matter generate secondary roentgen rays, and the effect of these secondary roentgen

6. Coolidge and Kearsley, Jr.: Am. J. Roentgenol., February, 1922, p. 88.

7. Krönig and Friedrich: Physikalische und biologische Grundlagen der Strahlen-therapie, 1918, p. 122.

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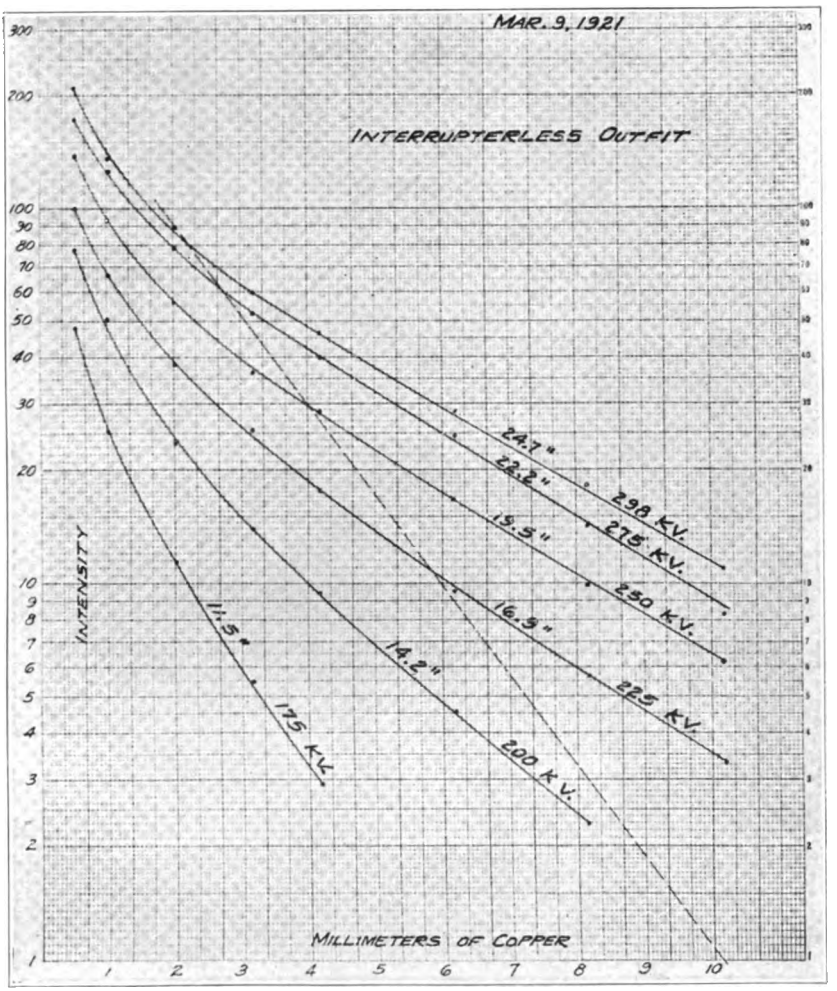

Fig. 7.—Absorption curves through copper filters.

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rays is added to that of the original beam. The greater the amount of matter subjected to the action of the original beam, the greater the amount of secondary rays generated, and, therefore, the greater the percentage depth dose. As has already been pointed out, the shorter the wave length of the roentgen ray, the greater the amount of rays which will pass through a certain amount of tissue. The combination of higher voltage and larger port of entry is, therefore, effective in increasing the percentage depth dose.

Roentgen-ray tubes and generating apparatus are now available for operation at voltages of 200,000 and some experimental work has been done at voltages of 300,000. The tube developed for this work is of the hot cathode type with solid tungsten target, similar to that used at lower voltages except that the bulb is slightly larger and the arms somewhat longer, to prevent arcing along the surface of the glass. Experience has shown that these tubes operate most satisfactorily when excited from a high tension transformer with mechanical rectifier, or from a constant potential continuous current machine.

As previously stated, the recent work of Ellis in England shows that we should get, at 400,000 volts, radiation similar to the gamma rays of Ra-B, and at 3,000,000, radiation similar to the gamma rays of Ra-C. Though we may not be able to go to 3,000,000 volts, we may well be able to go high enough to increase materially the amount of roentgen-ray energy which can be transmitted through different mediums.

CONCLUSIONS

1. Increasing the voltage applied to the roentgen-ray tube increases the intensity of the roentgen rays produced. The intensity of the more penetrating rays increases much more rapidly than that of the less penetrating rays.

2. At any definite voltage applied to the roentgen-ray tube, increasing the thickness of filter decreases the roentgen-ray intensity but increases the proportion of the more penetrating rays in the roentgen-ray beam beneath the filter.

3. With a definite thickness of any filter, increasing the voltage increases the ratio of depth to surface dose.

4. With a definite voltage and filter, increasing the target skin distance increases the ratio of depth to surface dose.

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5. Increasing the size of the port of entry increases the ratio of depth to surface dose.

6. Roentgen-ray tubes and generating apparatus are available for operation at 200,000 volts.

ABSTRACT OF DISCUSSION

Dr. William Allen Pusey, Chicago: We are under obligations to the physicists for introducing waves of higher voltage and shorter wave length but deeper penetration. Anyone who said such things are not useful would be stupid, but I would call attention to the fact that for the present these are technical, physical problems rather than problems in therapeutics. There is undoubtedly a propaganda for the use of roentgen-ray apparatus to produce enormous voltage. Many factors are involved in that problem about which we are uncertain. It is undoubtedly true that when we get more familiar with the use of roentgen-rays produced by such high voltage we will be able to attack deep lesions with more intelligence than we can now. I would, however, point out that in undertaking to treat these lesions with this new method we are not working with more intelligence than we have had. I know in the old days, when we treated with the old gas tubes, we were able to produce appreciable effects in deep lesions. I am sure no one who has seen a myoma of the uterus treated by this method will doubt that we could produce deep effects then. With the new apparatus, we have to know how much effect we are producing and how much effect we are getting. There is considerable difference in the opinion regarding this—one that the effect is produced by the direct voltage and the other that it is produced by the square of the voltage. We should keep an open mind and I think we are not yet in a position to be convinced that these enormous voltages are what we need. Recently I had the opportunity to see the work of Barlow with enormous doses of radium in animals. The deep effects produced in animals were exactly analogous with the effect produced on the skin by roentgen rays. They were so strikingly similar that you could almost use the one set of photomicrographs to illustrate the work. The chief thing that came to me in seeing this work of Barlow was the seriousness of an attempt to bombard a man's internals with this enormous penetration. I would not like to be regarded as undertaking to minimize the usefulness of the experiments presented today by Mr. Moore, but I would exercise the caution of a, perhaps, congenitally conservative man by saying that these questions before us are largely academic.

Dr. Harold N. Cole, Cleveland: I was much impressed with the fact that with a certain voltage, after you have used a certain amount of filter, no matter how much filter you use you get the same straight line of intensity. I should like to know about the amount of filter indicated with a machine with 60,000, one with 80,000 and one with 120,000 volts, respectively. This is a very important point and if you reach a certain amount of filter and no more will make any difference in the line, that is something we should know about.

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Dr. F. J. Eichenlaub, Washington, D. C.: As dermatologists, I am sure that we have learned a great deal from this paper. I think the facts brought out by Mr. Moore demonstrate that the dermatologist will never need the 200,000 volt machine. Furthermore, the statement that filtration decreases the intensity is very interesting, because it strengthens the plea of Dr. MacKee that the rays we want in dermatology are the unfiltered rays. In dealing with basal cell cancer, acne, and other diseases of the skin for which we use the roentgen rays, we want the unfiltered rays which give the greatest intensity in the superficial tissues.

Dr. William H. Guy, Pittsburgh: As dermatologists, we are, of course, vitally interested in the physical properties of roentgen rays, and are in sympathy with all attempts to improve apparatus and technical details. However, the bulk of our pathology is very superficial and we use by preference unfiltered rays with moderate powers of penetration, using the minimum amount that will prove effective. Heavy dosage of highly penetrating rays may produce deep seated vascular changes that are not only unnecessary but are also likely to be productive of late undesirable results. By increasing the distance between the anode and the skin, one may reduce the enormous disproportion between surface and depth dosage due to divergence of rays. When additional penetration is desired, filters are indicated. I am rather skeptical as to the highly touted value of these very high voltage machines; certainly in dermatologic practice they are not needed.

Dr. C. N. Moore, Schenectady, N. Y.: Any discussion of the particular results obtained by the use of low or high voltage is, of course, entirely out of my province. The answer to the question as to what type of rays produce the best results should be left to the physicians who apply the rays. One point I would like to correct in Dr. Pusey's discussion, and that is the impression that you may have roentgen rays so penetrating that they are not absorbed at all in going through matter. It is a physical fact that roentgen rays of any kind are absorbed to a certain extent. A definite thickness of matter will absorb a certain percentage of the rays and the next equal thickness will absorb the same percentage of those rays which were not absorbed in the first layer. In regard to Dr. Cole's question as to the proper thickness of filter to use at the various voltages employed in roentgen-ray work, it would depend on what intensity was desired beneath the filter. As you remember, the curves showing the relation between intensity and filter thickness for any definite voltage indicated that the intensity always decreased as the filter thickness was increased. The fact that the curves became straight lines beyond a certain filter thickness simply showed that further filtration did not change the quality of the roentgen-ray beam.

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THE TISSUE REACTION IN MALIGNANT EPITHELIOMAS OF THE SKIN

ITS VALUE IN DIAGNOSIS AND IN PROGNOSIS *

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A survey of the literature dealing with this particular phase of the cancer problem indicates that surprisingly little investigation has been made in this direction. It was Borst's opinion [1] that the parenchyma of the epithelioma is often retarded by the new connective tissue development roundabout. According to Unna's rule,[2] "The cellular infiltration of the cutis increases with the activity of the epithelial growth, when the epithelial margin is the seat of marked proliferation."

Concerning the presence of plasma cells, Aschoff, Ribbert and Borst say little. In 1891, Jadassohn [3] referred to the "encircling wall of plasma cells and leukocytes," and Unna,[2] describing the plasmoma of Paget's disease, characterizes it as "a bulwark of defense against cancer invasion." Reviewing a series of twenty-eight cases of epithelioma, Unna reports that fourteen contained many plasma cells, variously distributed, but often encircling the epithelioma. He also found numerous mast cells, usually in inverse ratio to the number of plasma cells present. The striking participation of the mast cell moved him to suggest that carcinoma should not be too widely separated from other chronic inflammatory processes. With Joannowicz,[1] he asserted that the rate of tumor growth is in inverse proportion to the number of plasma cells. Prytek [1] has studied a series of thirty-eight cases from

* From the Laboratory of the Department of Dermatology, Vanderbilt Clinic, Columbia University, New York.

1. Prytek: The Plasma Cells in Epithelioma of the Skin, Arch. f. Dermat. u. Syph. 120:611, 1914.

2. Unna: Histopathology (Walker's translation), New York: Macmillan Co., 1896.

3. Jadassohn: Verhandl. d. deutsch. Dermat. Gesellsch., Leipzig, 1891.

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Jadassohn's and other clinics, and he noted that the specimens with many mitoses often contained few plasma cells. However, he concludes that plasma cells, while not always present, "are often numerous, but bear no constant relationship to the type of neoplasm, nor to the presence or absence of ulceration, nor to the rate of tumor growth." From animal experiments, DaFano [4] has concluded that plasma cells as well as lymphocytes appear to be agents of the immunity process. McDonagh [5] believes that the plasma cell is present as an oxidizer of the deteriorating epithelioma cells.

Beginning in 1915, Murphy and his collaborators [6] of the Rockefeller Institute apparently showed the lymphocyte to be a bearer of tissue immunity against malignant invasion, upholding the views of DaFano in this respect. Itami [7] later claimed to have raised the immunity of animals against cancer by injecting lymph node extract. Mitoses have been reported as being very numerous in the spleen after tumor inoculation.[8] However, the work of Sittenfeld [9] and of Bullock and Rohdenburg,[10] the latter using splenectomized animals, tends to disprove the theories of DaFano and Murphy and to show that the lymphocyte, after all, is not necessarily the agent of immunity. Woglom [11] found that the spleens of immunized and inoculated rats were not enlarged; and Prime,[12] as the result of recent extensive observations, reaches the following conclusions: "Decreasing the circulating lymphocytes by small doses of roentgen ray does not render mice more susceptible to the inoculation of a spontaneous tumor from another mouse of the same strain. Mice with spontaneous lymphocytosis are not resistant to the implantation of a primary tumor from another mouse of the same strain." Thus far, animal experiments have

4. DaFano: Ztschr. f. Immunitätsforsch. u. exper. Therap., Orig. **5**:1, 1910.

5. McDonagh: The Epithelial Changes in Inflammation and Their Relationship to Malignant Epithelioma, Arch. f. Dermat. u. Syph. **120**:289, 1914.

6. Murphy, J. B.: J. Exper. M. **22**:204, 1915; **25**:609, 1917; **29**:25 (Jan.) 1919. Murphy, J. B., and Nakahara, W.: J. Exper. M. **31**:1 (Jan.) 1920.

7. Itami: J. Cancer Res. **4**:23 (Jan.) 1919.

8. Murphy, J. B., and Nakahara, W.: Footnote 6, fourth reference.

9. Sittenfeld, M. J.: J. Cancer Res. **2**:151 (April) 1917.

10. Bullock, F. D., and Rohdenburg, G. L.: J. Cancer Res. **2**:455, 465 (Oct.) 1917.

11. Woglom: J. Cancer Res. **4**:281 (July) 1919.

12. Prime, F.: J. Cancer Res. **6**:1 (Jan.) 1921.

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been limited to work with epitheliomas of the prickle cell type, only one case of basal cell epithelioma, occurring in a rat, having been reported.[13]

Here and there throughout the literature, the apparent relationship between chronic inflammation and the development of epithelioma is alluded to, some authorities stating that, without previous chronic inflammation, cancer does not exist (Billroth's dictum). According to McDonagh,[5] the occurrence of epithelioma follows a chronic inflammation, which produces lipoid-globulin substances in the cells.

With the purpose of further investigation, we have examined the slides from 100 human epitheliomas, noting the following points in each: the type of the tumor, whether basal or prickle cell; its apparent age and rate of growth; the depth of its extent into the underlying corium; the appearance of the cells of the tumor parenchyma and the number of mitotic figures observed; the state of the overlying epidermis, whether thinned or acanthotic; and the characteristics of the stroma, including the connective tissue degeneration, its degree, location and type (whether hyaline or basophilic), the growth of new connective tissue, and the types and relative numbers of the plasma cells, lymphocytes and polymorphonuclear leukocytes, their relation to the blood vessels, and the condition of the vessel walls, especially as to the presence or absence of hyaline degeneration. The specimens had been fixed in Bouin's solution and stained with hematoxylin and eosin; a few were stained with hematoxylin orange and acid fuchsin. Fifty of the specimens were from basal cell epitheliomas, while the remaining fifty were of the prickle cell variety, all stages of development and various rates of growth being represented. The basophilic degeneration noted was of the so-called mucoid type, such as that occurring in senile atrophy of the skin, and the hyaline or acidophilic degeneration was that which accompanies chronic interstitial inflammation; its location in the derma was noted, and the locations in which each type of degeneration predominated, whether immediately beneath the epidermis or deeper. The stain did not permit an examination for mast cells, nor could the elastic tissue be studied. The results have been tabulated as shown in Table 1, presenting the findings in each case, and these findings have been summarized in Table 2.

13. Morris, D. H.: J. Cancer Res. 5:147 (April) 1920.

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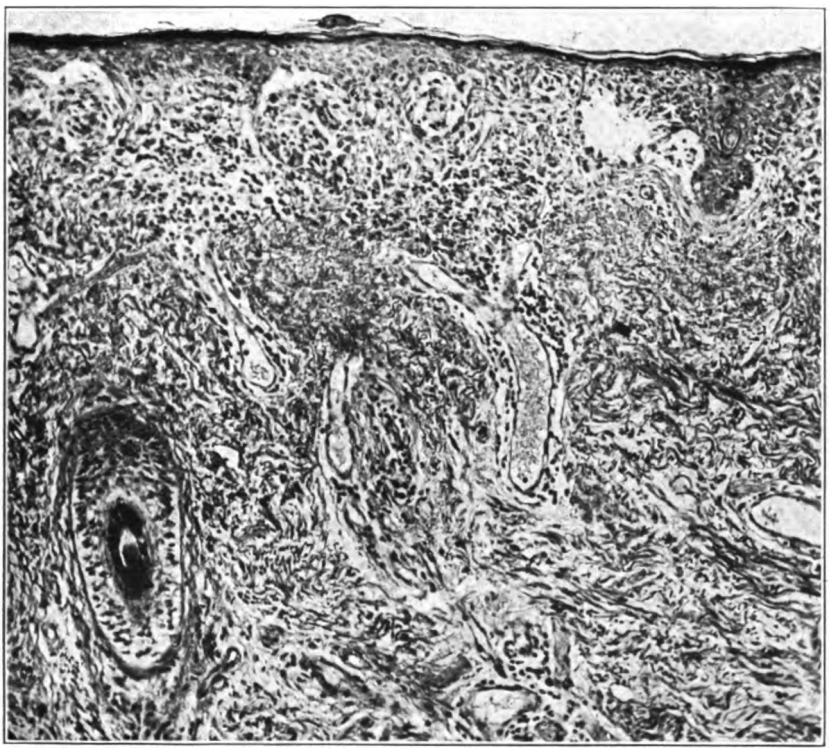

Fig. 1.—Neoplasms of the epidermis, associated with thinning of the remaining epidermis and not accompanied by a chronic inflammatory process, are usually basal cell epitheliomas; compare Slide 16.

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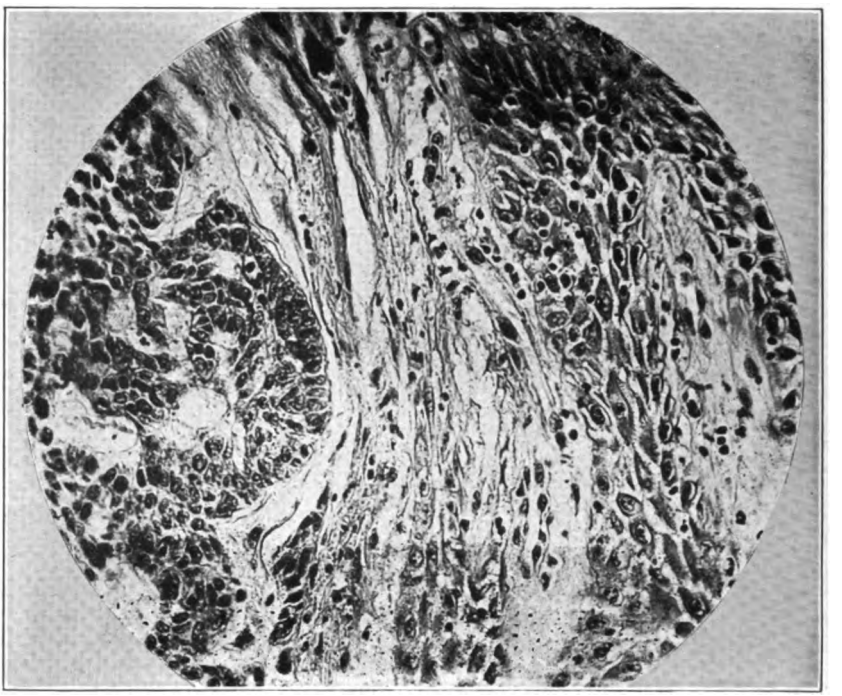

Fig. 2.—If these basal cell epitheliomas are slow growing, they usually present slight inflammatory tissue reaction, with lymphocytes as the predominant cells; compare Slide 18.

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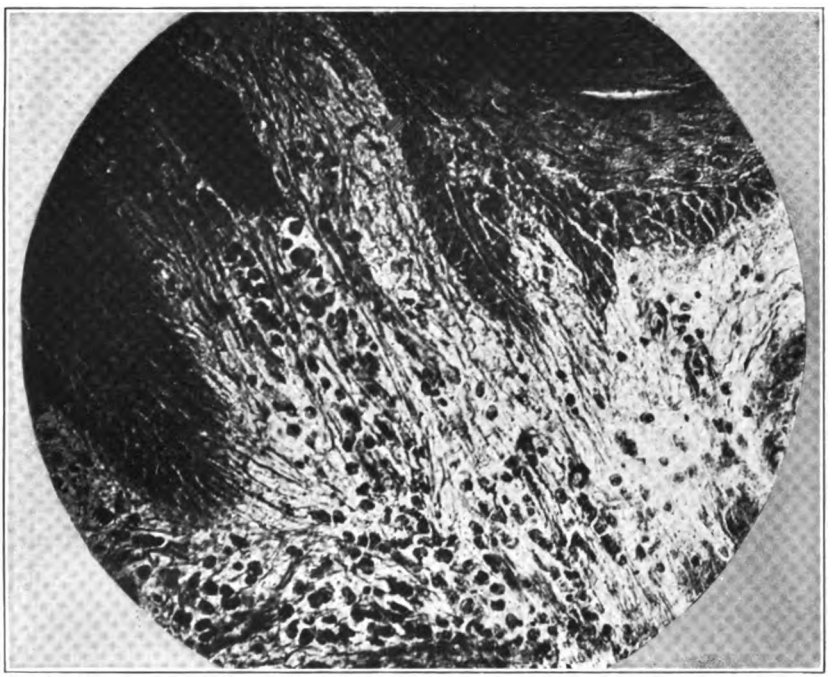

Fig. 3.—If a basal cell epithelioma is accompanied by much tissue reaction, we find a mixture of lymphocytes and plasma cells; compare Slide 12.

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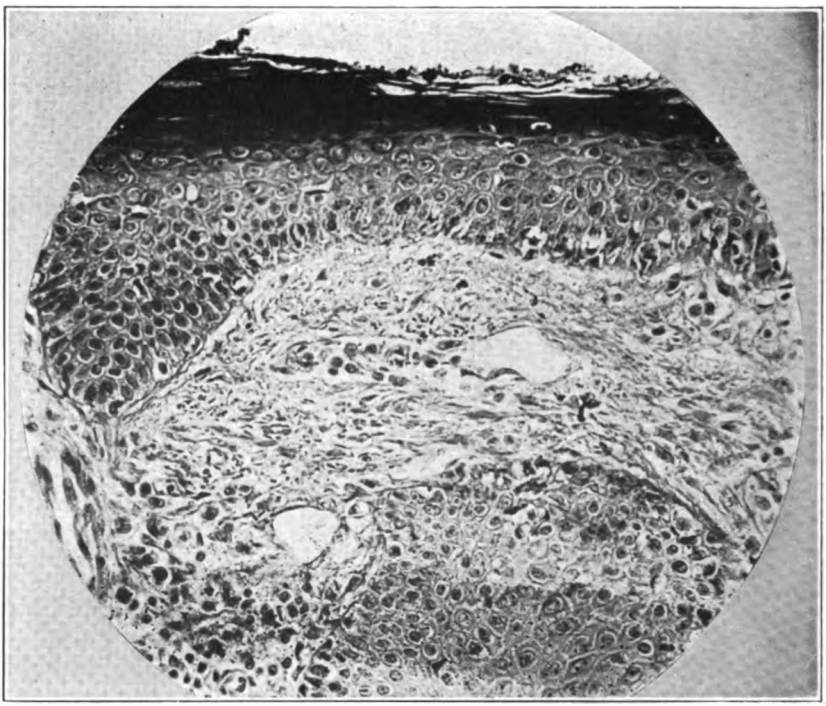

Fig. 4.—When a basal cell epithelioma is slow growing, as a rule we find little evidence of connective tissue degeneration, and vice versa; but there is always some connective tissue degeneration. In basal cell epitheliomas, the type of connective tissue degeneration is prevailingly basophilic rather than hyaline; compare Slide 5.

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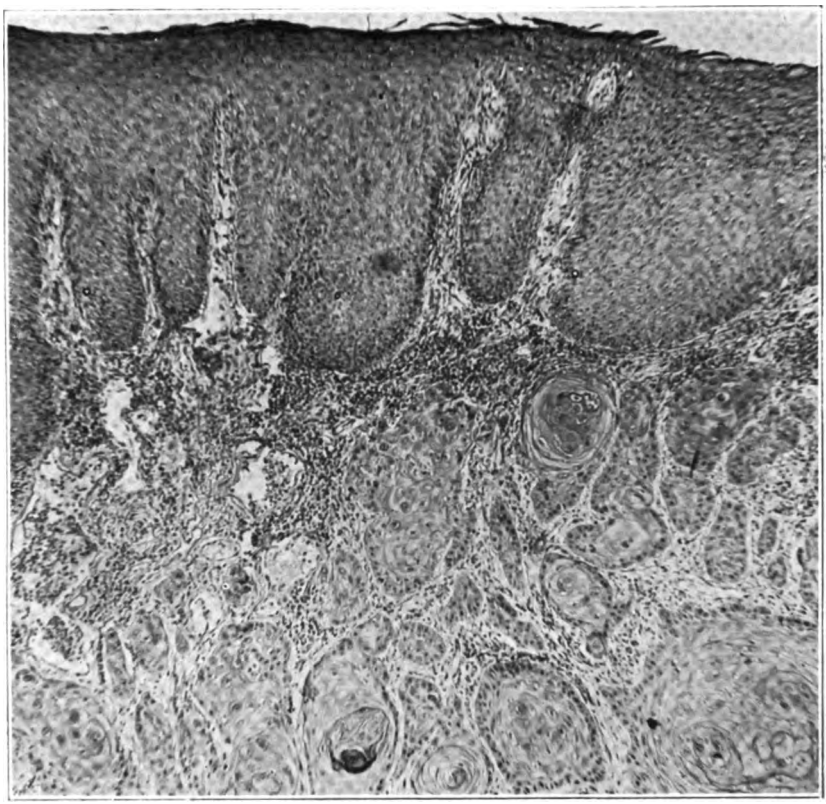

Fig. 5.—The prickle cell epithelioma is always associated with evidences of a chronic inflammatory process, for example, acanthosis or hyperkeratosis; compare Slide 59.

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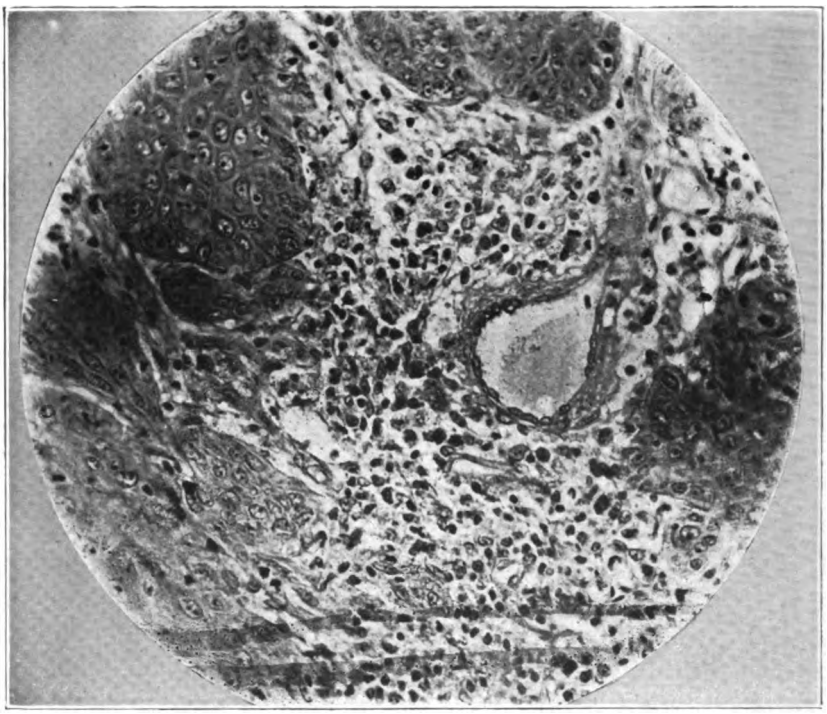

Fig. 6.—This chronic inflammatory process has ordinarily been present for a long time, so that the tissue has had time to develop a certain amount of resistance, as evidenced by the proliferation of connective tissue, by the presence of plasma cells, and by changes in the blood vessels; compare Slide 7.

The slow development of a prickle cell epithelioma is accompanied by the appearance of plasma cells (Slide 7).

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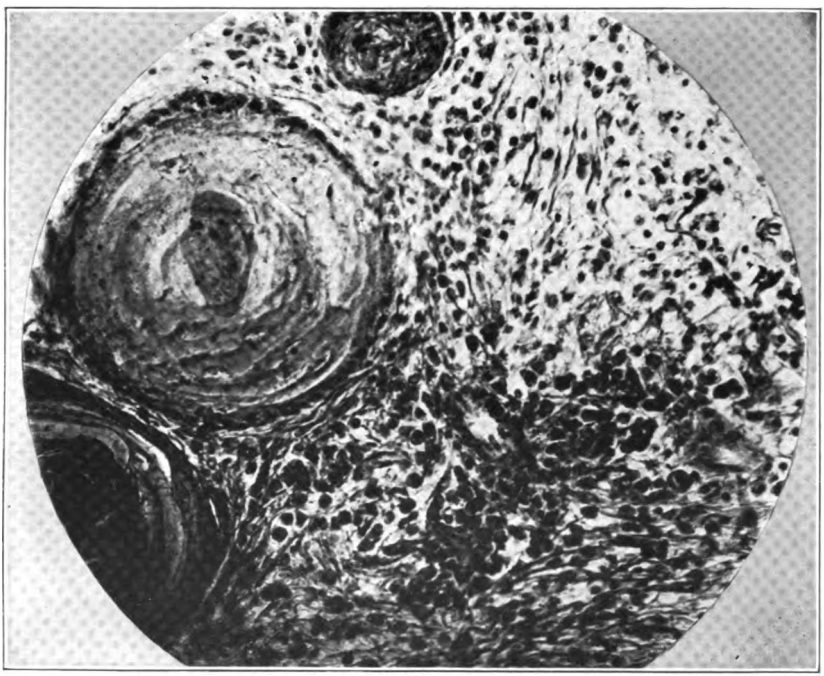

Fig. 7.—This preceding chronic inflammatory process is a complicating factor, according to the nature of its pathologic picture; compare Slide 93.

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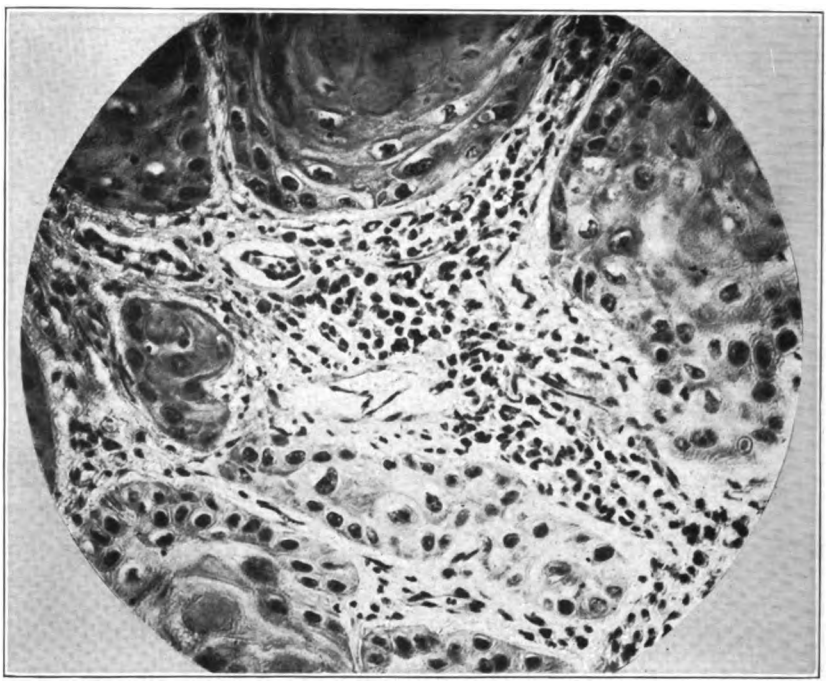

Fig. 8.—Connective tissue degeneration in prickle cell epitheliomas is more hyaline than basophilic, as a rule; compare Slide 98.

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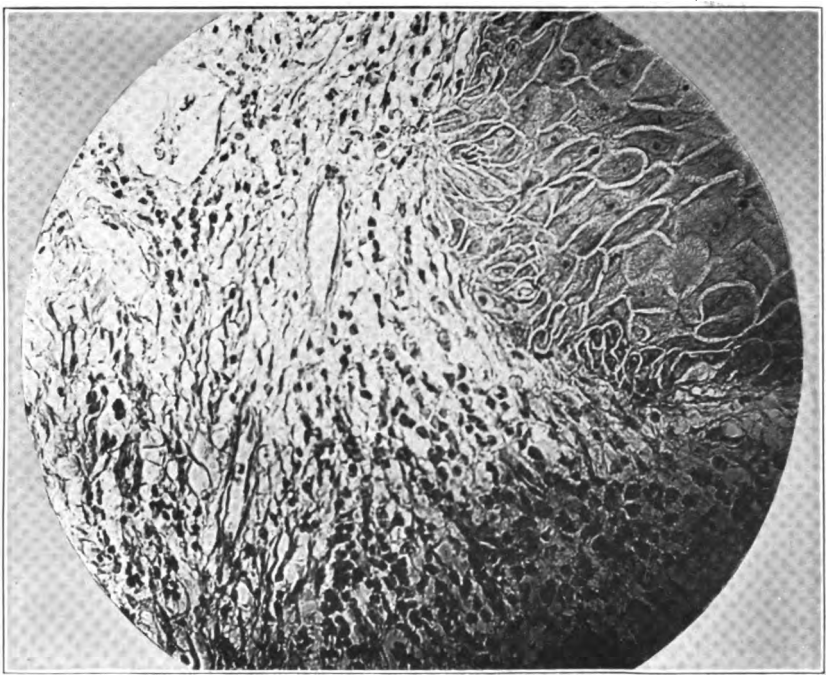

Fig. 9.—The rapid development of a prickle cell epithelioma is accompanied by lymphocytes; compare Slide 1 (Highman).

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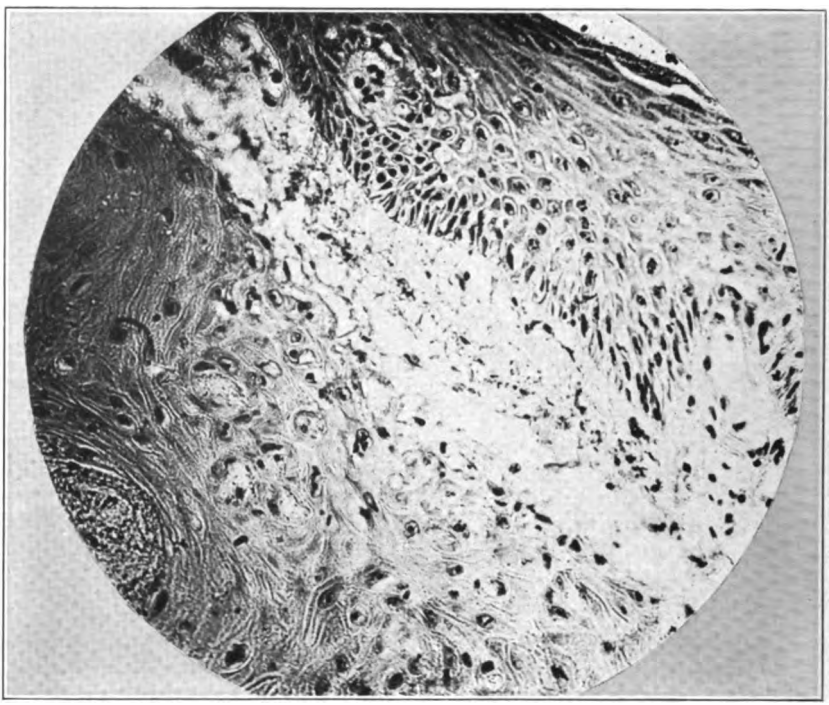

Fig. 10.—The number of plasma cells and, to a somewhat less extent, the number of lymphocytes, vary directly with the amount of hyaline degeneration of the connective tissue. Here it is slight.

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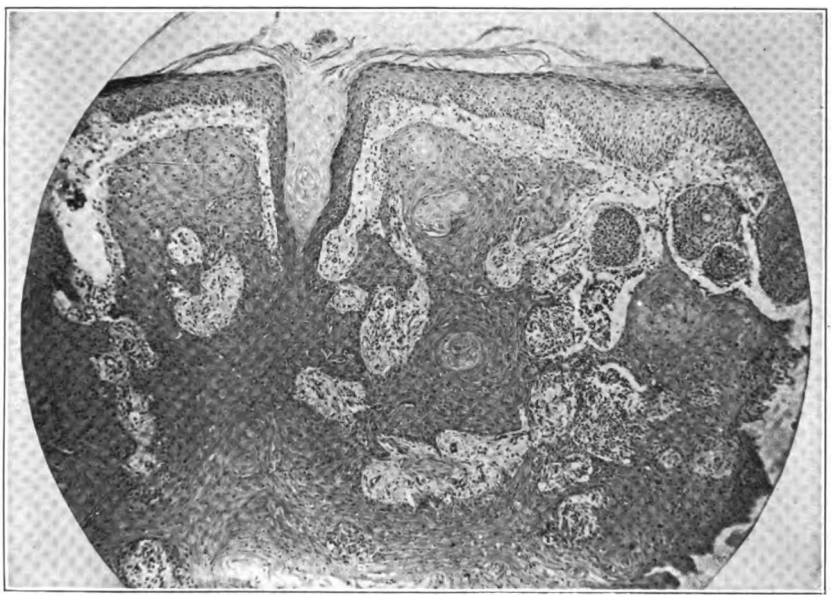

Fig. 11.—A typical prickle cell epithelioma; compare Slide 28.

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TABLE 2.—AN ANALYSIS OF THE FINDINGS IN FIFTY PRICKLE CELL AND FIFTY BASAL CELL EPITHELIOMAS

Findings	Basal Cell		Prickle Cell	
	Typical	Otherwise	Typical	Otherwise
Epithelioma arising from thin epidermis	24	..	..	..
Signs of a preceding inflammatory process	..	45	50	..
Noninflammatory	5	..	..	..
Epidermis acanthotic	..	8*	45	..
Epidermis thin	35	..	..	..
Infiltration of lymphocytes alone	21	..	..	17
Lymphocytes and plasma cells	..	27†	..	35‡
Infiltration of plasma cells alone	..	..	..	..
Cellular infiltration perivascular	..	4	19	..
Connective tissue degeneration basophilic only	5	..	..	..
Connective tissue degeneration basophilic and hyaline	..	41	..	34
Connective tissue degeneration hyaline only	..	2	15	..
Connective tissue degeneration in upper corium basophilic only	18	..	..	..
Connective tissue degeneration in upper corium basophilic and hyaline	..	20	..	20
Connective tissue degeneration in upper corium hyaline only	..	..	26	..
Hyaline changes in vessel walls	..	..	19	..
Fibrosis	..	44§	..	40§
Mitoses in epithelioma cells	..	45¶	..	48¶
Epithelioma cells of hardy appearance	..	46	..	47
Epithelioma cells of faded appearance	..	2	..	3

* Cylindromas, nevi, etc.
† Plasma ++ in seventeen.
‡ Plasma ++ in twenty-one.
§ Fibrosis ++ in thirteen.
¶ Mitoses ++ in six.

RESULTS OF OBSERVATIONS

1. Neoplasms of the epidermis, associated with thinning of the remaining epidermis and not accompanied by a chronic inflammatory process, usually are basal cell epitheliomas (Fig. 1).

2. If these basal cell epitheliomas are slow growing, they usually present slight inflammatory tissue reaction, with lymphocytes as the predominant cells (Fig. 2).

3. If a basal cell epithelioma is accompanied by much tissue reaction, we find a mixture of lymphocytes and plasma cells (Fig. 3).

4. When a basal cell epithelioma is slow growing, as a rule, we find little evidence of connective tissue degeneration, and vice versa; but there is always some connective tissue degeneration (Fig. 4).

5. In basal cell epitheliomas, the type of connective tissue degeneration is prevailingly basophilic rather than hyaline (Fig. 4).

6. The prickle cell epithelioma is always associated with evidences of a chronic inflammatory process; for example, acanthosis or hyperkeratosis (Fig. 5).

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7. This chronic inflammatory process has ordinarily been present for a long time, so that the tissue has had time to develop a certain amount of resistance, as evidenced by the proliferation of connective tissue, by the presence of plasma cells, and by changes in the blood vessels (Fig. 6).

8. This preceding chronic inflammatory process is a complicating factor, according to the nature of its pathologic picture. (Fig. 7: prickle cell epithelioma in tissue affected by lupus vulgaris.)

9. Connective tissue degeneration in prickle cell epitheliomas is more hyaline than basophilic, as a rule (Fig. 8).

10. The rapid development of a prickle cell epithelioma is accompanied by the presence of lymphocytes (Fig. 9). The slow development of a prickle cell epithelioma is accompanied by plasma cells (Fig. 6).

GENERAL CONCLUSIONS

1. The number of plasma cells and, to a somewhat less extent, the number of lymphocytes, vary directly with the amount of hyaline degeneration of the connective tissue. (Compare Figure 10, showing a slight amount, and Figure 8, showing a great amount.)

2. The apparent strength of the cancer cells and the number of mitoses bear no constant relationship to any other feature, nor to each other.

3. Mitotic figures may be entirely lacking, and they are usually not so numerous as might be expected.

4. The number of plasma cells in prickle cell epitheliomas varies directly with the number of pearls, as a rule.

5. Plasma cells are never found in the absence of hyaline degeneration.

6. As the number of plasma cells is an indication of the degree of resistance (immunity) of the tissue (derma), the malignancy of the neoplasm varies inversely in proportion to the number of plasma cells. The more malignant the process, the less the number of plasma cells, showing that the neoplasm is developing so rapidly that the tissue has not the time to develop any resistance. (This is a note of prognostic value.) (Figure 4 represents a typical basal cell epithelioma, and Figure 11 a typical prickle cell epithelioma.)

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EXPECTANCY IN ROENTGEN-RAY TREATMENT OF SKIN LESIONS FROM THE PATHOLOGIC STANDPOINT

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NEW YORK

Skin lesions of the most diversified types, unrelated in causation and structure, respond to treatment with the roentgen rays. Conversely, lesions apparently related will often show varied responses to this peculiar agent. Nothing could be more completely unrelated than a basal cell epithelioma and a psoriasis lesion, and yet they resolve under irradiation. Psoriasis and parapsoriasis are apparently cousins under the microscope, but parapsoriasis is uninfluenced by the roentgen rays. Acne, with no apparent anatomic similarity to any of the foregoing conditions, affords one of the most brilliant examples of responsiveness to roentgenotherapy. What is there to reconcile the implied divergencies?

Reflection will reveal that there are a sufficient number of common denominators to relate these phenonema in nearly all instances. Certain effects of the roentgen rays are understood. It is known that in varying doses they either stimulate, inhibit or destroy the reproductive property of cells. This is particularly true of embryologic cells, reproductive cells, secretory cells and certain groups of abnormal cells, whether inflammatory or neoplastic. It is also known, as would follow from their effect on secretory cells, that the roentgen rays diminish or entirely destroy gland function.

In overdosage, the roentgen rays attack particularly elastic tissue, glands and the normal proliferative power of the skin. Through their effect on the elastic tissue, there are two distinct results; the arterioles lose their elasticity and the corium tends to atrophy. In a word, one of the striking morbid effects of the roentgen rays on the skin, is to produce artificially, from beginning to end, a series of events absolutely paralleling the picture of scleroderma. Should the destruction be slight, no permanent damage is done; should it be severe, even necrosis may take place. At the same time that these changes develop, the sweat

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glands, oil glands and hair papillae shrink or entirely disappear, the skin thus becoming dry and brittle. Pigmentation of the skin and keratoses, either due to the roentgen rays or byproducts of their effect, supervene, the keratoses at times terminating malignantly. We thus have artificially produced by the roentgen rays a second great skin picture closely paralleling that of xeroderma pigmentosum.

For the practical student in this field, then, it is important to remember that overdosage with roentgen rays, according to its degree, will produce a simple picture of transitory erythema, mild atrophy, restricted or extensive necrosis, or one reminiscent of scleroderma, or, finally, of xeroderma.

DOSAGE

To prevent any of the foregoing disasters, sincere efforts have been made to determine the minimum quantity of radiation that will produce the maximum therapeutic effect. In the entire history of this subject, no one has done more to place roentgen-ray treatment of the skin on a firm, safe and intelligent foundation than MacKee. After Kienboeck had reestimated dosage by means of placing the Sabouraud pastil on the skin, instead of half way between the skin and the target, it was MacKee, working with modern apparatus, who elaborated a completely successful technic. At first, he did so by means of the Holzknecht radiometer, but later he was able to abandon this because it had been established that under known constant factors, namely, voltage, milliamperage, distance and time, definite quantities of roentgen rays could be applied.

It had been determined that from four to five of Holzknecht's units (4-5H) corresponded to the scalp depilating dose called Tint B on the Sabouraud scale. Since the intensity of the rays varies inversely as the square of the distance, it took four times as long to discolor the pastil placed on the skin, as by the half distance method. This was arbitrarily called the Holzknecht unit, skin distance (H.s.d.). As a result, the symbol 1 H in this country means four or five times the dose it represents abroad, and great confusion has been created. For all practical purposes, 1 H s.d. equals the erythema dose except on the scalp, where one and a quarter H s.d. are required to produce erythema. It would simplify matters to substitute the letter E. for H s.d., the E being an abbreviation for erythema. Since E might be an abbreviation for epilation as well, and since MacKee has been the greatest student of

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the subject under discussion, it seems that the symbol M should be adopted to represent the erythema dose, under the conditions included in the symbol 1 H s.d.

Thus one-quarter M would equal a fractional dose, 1 M a massive dose, etc., according to MacKee's terminology. It is a pity that MacKee used so many fanciful expressions in describing his dosage, instead of simply adhering to the numerical units of measure. The words hyper-intensive, superintensive, intensive, fractional and the like, convey nothing uniform to different minds; whereas, the figures and symbols, which he uses synonymously, do. For this reason, it is to be hoped that in the future, whether the symbol of the erythema dose remains 1 H s.d., 1 M, or 1 E, the gradations will be expressed numerically and not verbally.

From this article, the method of determining dosage, a discussion of the different types of apparatus, the various radiometers, and all kindred topics will be omitted, partly because of lack of space and partly because the subjects are all well known, and are so thoroughly discussed in MacKee's work that a recapitulation would be presumptuous.

THERAPEUTIC AIMS AND SCOPE

The object of this article is to outline what the roentgen rays may be expected to accomplish with different skin lesions, regarded from the standpoint of morbid anatomy and normal or abnormal cutaneous function. In addition, their therapeutic value from the purely mechanical standpoint will be discussed.

In general, a lesion may be considered the result of the response of tissue to a pathogenic agent to which it is peculiarly susceptible. Cures, except in the domain of surgery, are produced either by eliminating or by destroying the pathogenic agent, or by so altering tissue as to render it unable to respond to the pathogenic factor or factors. In the treatment of epithelioma, probably the former mechanism is illustrated, because of the destruction of the malignant cells themselves, or of the destruction, primarily, of the conditions which favor their growth. In acne, on the other hand, the second state of affairs is illustrated; for acne is a disease of puberty. By irradiation, the skin is so altered that it can no longer respond in that abnormal manner, clinically designated as acne; whereas, the underlying forces, assembled in the mechanism designated as puberty, persist until adult life. Crude as this illustration

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is, it nicely elucidates the points. The mechanical use of the roentgen rays is illustrated in the cure of ringworm of the scalp by epilation. Here, the falling of the hair, with the resultant mechanical removal of the fungi, produces the cure, not the effect of the roentgen rays on the fungi themselves.

It will not be possible in all types of lesions so precisely to indicate the effect of the roentgen rays as in the foregoing examples. The groups of conditions in which the roentgen rays are efficacious are simple inflammations, infections, noninfectious granulomas, dystrophies, benign new growths, malignant new growths and certain nevi. In short, some lesions in the entire range of dermatoses are amenable to the roentgen rays. The factors are unknown which determine the susceptibility of one lesion and the insusceptibility of its nearest relative to this mode of treatment, even though anatomically there may be only the slightest difference between the two. For example, some forms of tuberculosis respond readily. Syphilis does not. Here the causative parasites are as wide asunder as the animal and vegetable kingdoms. But lepra does not either so far as we know, and the lepra bacillus and tubercle bacillus are remarkable for their similarity in appearance and staining properties. But further, not all forms of cutaneous tuberculosis respond equally readily. What determines these variations would be pure speculation if the answer were sought today.

As briefly as possibile, then, will be discussed the lesions that respond or do not respond to roentgen-ray treatment; the probable explanation of the phenomena, based on histology, and finally, in some instances, the best dosage for the given lesion. It is understood that the hypotheses advanced are merely tentative and that we are postulating no dogma, but will gladly welcome any evidence the future may unveil, either for or against our beliefs. The dosage will be given in terms of the letter M, following which will appear the symbol (H s.d.). It is hoped that this new symbol will find favor among Americans, partly in recognition of MacKee's work, and partly because it will remove confusion. It is further hoped that the views advanced will furnish a modest basis for an intelligent conception of roentgenotherapy of the skin.

GENERAL CONSIDERATIONS

It is not so important as one would imagine from the literature whether filtered or unfiltered rays are used, or whether several short

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or fewer long exposures are made. There are, of course, many specific instances in which this statement does not apply. But for the purposes of this article, the discussion involved would have to be too long. Thus, in subsequent paragraphs certain beliefs will be more or less arbitrarily stated. In general, however, not a single enthusiasm expressed by MacKee in his recent work, not a single one of his qualifications fails of corroboration in our experience. This indicates our views on the problems inherent in the foregoing.

We wish to disclaim the impression that we regard roentgenotherapy as the only way of treating disturbances of the skin. Today, however, it is undoubtedly the most important single method of managing such diseases. When the attempt to apply our gleanings from investigations in altered biochemistry or endocrine disbalance have failed to make a skin lesion disappear, roentgenotherapy often succeeds. It is admitted that our studies of the causation of skin diseases must continue and are of first importance; for no one claims that any other method of approach to the problem of curing disease is rational. But while our investigations proceed, and until they are fruitful, we must use the best available symptomatic methods for relieving the sick; and so far as the skin is concerned, as stated, roentgenotherapy affords the greatest possible hope.

As we particularize in the following paragraphs, in each condition discussed, when possible, its etiology will be given, its pathology, the volume of the lesion and the best method of administering irradiation, together with the prognosis under such treatment. Not every skin disease that has been successfully managed by the roentgen rays will be included. Unless there is a special reason, only the commoner ones will be mentioned.

SIMPLE INFLAMMATIONS

For want of a better term, under simple inflammations we classify those cutaneous catarrhal reactions of which the causation is unknown. The range of this group is from simple determatitis to lichen planus, and the primary and secondary lichenifications. The main groups to be discussed are simple dermatitis, implying eczema, the psoriasiform dermatoses and the lichens.

Dermatitis has so many causes that it is not astonishing that the condition, however constant in aspect, shows no uniform response to roentgenotherapy, any more than to any other form of treatment. In

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general, the disease is due to an interoperation between external and internal factors; but in spite of this the attempt to alter the reacting properties of the skin by means of the roentgen rays is not invariably successful. Pathologically, the condition is an exudative catarrh, acute, subacute or chronic. When the cause is known, as in dermatitis venenata, there is no object in using the roentgen rays, for the cure is obvious. In obscure cases, whether in the vesicular or in the scaling phase, the roentgen rays are valuable in doses of from one-eighth to one-quarter M (H s.d.), repeated at weekly intervals for from four to even ten exposures, with the normal surrounding skin screened. In extensive eruptions, different parts of the body should be irradiated on as many days as feasible without producing leukopenia; but the same area should not be exposed more than once a week. The lesions in question are superficial and in general show relatively slight alterations in the epidermis, edema, and not profound infiltration in the upper half of the corium. The dose mentioned is probably only sufficient to inhibit the tendency in the epidermis to hyperplasia, and to destroy the deeper inflammatory cells.

In the squamous form, the process is partly as outlined in the foregoing, but there is more marked hyperkeratosis and parakeratosis, with distinctly more fixed connective tissue cells in the infiltration, and hence the need for at least one quarter M per week to each area. Otherwise, the remarks in the preceding paragraphs also apply here.

In forms of dermatitis due to fungi, the radiation does very little good until after the organisms have been destroyed, although a slight degree of inhibition may be ascribed to the rays. In varieties due to excessive secretion of the sweat glands, and in those whose basis is seborrhea, the rays are of value in their effect on the lesions and in their inhibitory effect on gland function. In cases of undetermined etiology, the rays sometimes work and sometimes do not; but it is difficult to forecast the result. It is equally difficult always to state what the expectancy of success is; but in the vast majority of cases the lesions disappear and remain away for a variable period, in a striking number, apparently permanently. When they have disappeared, they return only either when the effect of the rays on the skin has worn off, or when, because of the interruption of general treatment, the original conditions determining the disease have been reestablished.

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Other vesicular and bullous diseases do not respond encouragingly to the rays, although there are reports of cures of simple herpes in the literature.

PSORIASIFORM DERMATOSES

The type of this group is psoriasis. The cause of the disease is unknown. It is obviously due either to a metabolic disturbance or to an external infection. The lesions vary in size and shape, and under the microscope show distinct changes in the epidermis and corium. A psoriasis lesion may be from 1 millimeter to three eighths of an inch thick, and the latter is covered by a dense scale of hyperkeratotic and parakeratotic tissue. There are numerous mitoses. The infiltration consists mainly of small round cells of the lymphatic type, with a variable number of fibroblasts. The object of roentgen-ray treatment is to inhibit epidermal hyperplasia and promote resorption of the inflammatory deposit. The rationale of this is a direct attack on the multiplying cells of the rete and small round cells in the infiltration, which, probably by analogy with lymphocytes, are vulnerable to the rays. The main technical difficulty lies in the fact that the scale acts as a screen in direct ratio to its thickness. The majority of lesions disappear under intelligent treatment. Some are inexplicably obstinate and, if unresponsive after six exposures, the attempt to remove them by means of roentgen rays should cease. The management is precisely as in the squamous form of dermatitis. Acute early attacks are unfavorable for the roentgen rays. Coincident with irradiation, general treatment should be pressed, but local irritating applications are contraindicated.

Related dermatoses vary in their response. Seborrhea does particularly well. Parapsoriasis, which is not as intense a process by one-twentieth as psoriasis, does not respond at all. No one can explain the reasons. Properly employed, the roentgen rays may be used in psoriasis and seborrhea of the scalp, but for not more than from four to six weekly exposures of one quarter M (H s.d.), employed by the regional method used in scalp epilation; epilation should never be produced. Obviously psoriasis recurs, although we have one case on record in which there was no relapse after seven years.

LICHENS AND LICHENIFICATION

Lesions in this group are characterized by profound infiltrations and marked epidermal changes. In lichen planus, the epidermal changes

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are relatively less intense than in lichenification, although the infiltrations are equally voluminous in the two groups. In acute lichen planus and in many of the chronic subvarieties, roentgen-ray therapy appears to be almost a specific, both as to the disappearance of the lesions and as to the control of itching. The infiltrating cells resemble lymphocytes, admixed with melanoblasts. The latter persist long after the papules have clinically disappeared, and the roentgen rays have no influence on the remaining pigmentation. The treatment is carried out as in universal psoriasis, or, for restricted lesions, one quarter M (H s.d.) is given weekly, although in hypertrophic forms higher doses must be employed. In nearly all generalized cases the patients recover more rapidly under this treatment than under any other, and at least 75 per cent. of the other types of lichen planus respond. When the mouth is involved, of course, the use of roentgen rays is inconvenient.

In lichenification, whether primary or secondary, small doses of roentgen rays cure three quarters of the cases, except when an underlying dermatosis not amenable to the roentgen rays exists. Under these circumstances, the main consideration is to eliminate the underlying state.

None of the other conditions bearing the name lichen seem amenable to the rays.

PRURIGO

Prurigo is probably papular urticaria. At times, it responds well to small repeated doses of roentgen rays. The lesions consist of infiltrations of round cells, below an epidermis which is slightly vesicular. The disease is metabolic, and the skin is not capable of change under the roentgen rays sufficient to render it irresponsive to the internal disturbance. The lesions disappear rapidly enough in favorable instances, but recur. There is a transient influence but nothing definite. Obviously, the agent would not be employed in the erythema and urticaria groups related to prurigo. Not even in erythema nodosum would there be any indication for its employment.

INFECTIONS

The roentgen rays are apparently of no use in skin diseases caused by animal parasites of any variety. Neither are they of value in superficial, bacterial or fungus infections. In fact, there seems to be no disease primarily due to pus cocci in which the use of roentgen rays has

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been successful. In acne, in which the pustulation is incidental, the roentgen rays are effective because they stop the formation of comedones. In ordinary sycosis, as well as in that due to fungi, the value of the roentgen rays resides in the removal of the germs by producing falling of the affected hairs. On the other hand, in bacillary diseases and even in those due to fungi, the roentgen rays are of great value when the lesions are granulomas, the one notable exception being lepra. Syphilis is not included because it is due to a protozoon, and in this condition there would be no particular reason for using the roentgen rays.

Infections Due to Cocci—Nonparasitic sycosis is treated by a depilatory dose and the cure is due to falling of the affected hairs. Acne is not essentially a pus disease. It is a manifestation of puberty, and is the result of follicular hyperkeratosis and overactivity of the sebaceous glands. If the functional disturbance can be controlled and the hyperkeratosis stopped, abscess formation will automatically cease. This can be accomplished by the roentgen rays, administered according to the MacKee technic, in at least 95 per cent. of all patients. In this article, acne has again been mentioned at this point, because its striking clinical feature is the presence of pustules. In general, pyodermas are not affected by the roentgen rays.

Infections Caused by Bacilli.—Lupus vulgaris, tuberculosis verrucosa cutis and many other forms of tuberculosis of the skin will disappear under from one to three irradiations of 1 M (H s.d.) at intervals of four weeks. The result is possibly due to some effect on the micro-organisms, but probably the correct explanation is that the granuloma is absorbed through the direct influence of the rays on the inflammatory cells.

Except in erythema induratum, the tuberculids are not often influenced by the roentgen rays. This is difficult to explain, for nearly all of this group of lesions are small granulomas. Erythema induratum yields to one quarter M (H s.d.) applied weekly, or larger doses applied at longer intervals. In England, lupus erythematosus is treated by this means. We have not attempted to verify the reports by test, because lupus erythematosus microscopically shows dilatation of the vessels and destruction of the elastic tissue, and ends in atrophy. Since these effects can all be produced by the roentgen rays, their use in this disease seems

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unsound. Next to the Finsen lamp, the roentgen rays afford the greatest promise in skin tuberculosis.

Why they are not effective in lepra, or whether not enough studies have been made, cannot be stated; nor have we any personal experience with sarcoid. In rhinoscleroma, the roentgen rays are invaluable, but we cannot speak from personal experience.

Fungus Infections.—In sporotrichosis, blastomycosis and actinomycosis, the roentgen rays are almost a specific, unless the systemic involvement is too great; and, even in this event, the lesions themselves often may be caused to disappear. The treatment is carried out as in tuberculosis. Resorption of the lesions is evidently due to the direct effect of the rays on the infiltrating cells.

In ringworm of the scalp, with and without kerion, and in favus, the value of the rays lies in their depilating action, when properly administered by the Kienboeck-Adamson method, with the MacKee system of dosage. This, perhaps, constitutes the only rational treatment for these diseases. In ringworm of the nails, in which the rays are often valuable, the way in which they work is not understood.

NONINFECTIOUS GRANULOMAS

This group of conditions includes mycosis, leukemia and Hodgkin's disease. The relation of these conditions to lymphosarcoma is not clearly understood; but the fact remains that their lesions are highly responsive to roentgen rays administered in doses of from one-half to three-quarters M (H s.d.), or even slightly more, at suitable intervals. To all intents and purposes, the lesions are new growths, and are probably subject to the laws governing the effect of roentgen rays on young growing cells. Of course, treating the skin lesions successfully does not cure the disease, but merely temporarily removes its manifestations. No other method of attack affords so much promise, so far as symptomatic therapy is concerned.

NEW GROWTHS

In new growths, the roentgen rays are inconsistent in action. They are far more effective in malignant than in benign types. In benign connective tissue neoplasms, except at times in keloids, they are useless. In benign epithelial growths, except in the ordinary wart, of which about 60 per cent. are responsive, they are likewise useless, unless

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plantar warts are included. In malignant neoplasms, whether sarcoma or epithelioma, the roentgen rays are of extraordinary value. The majority of such lesions will disappear after one irradiation with from one and one-half to two M (H s.d.). Often further treatment is required, but it is not within the province of this article to enter into technical details. Nowhere is the value of roentgen-ray therapy better illustrated than in this field. The relative merits of roentgen rays and radium are not part of the subject under discussion, so they will not be mentioned. Nor do we wish to champion the roentgen rays to the exclusion of other recognized methods of treatment. To consummate a victory in battle, all forces are employed; and, in the war on malignant new growths, the roentgen rays constitute a valuable force. The attack is a direct one on the malignant cells, which, being young and rapidly reproductive, are far more vulnerable than the maturer, less rapidly growing cells of benign neoplasms.

Nevi, which might well be included under neoplasms, since they are growths due to intra-uterine anomalies, whether evidenced at birth or in later life, are so rarely amenable to roentgen-ray treatment as to require no discussion in this brief article. On the whole, they are highly organized and rather mature lesions. Some of them are capable of giving rise to malignancy, and if this occurs, the resultant growth can often be successfully treated by the roentgen rays.

The so-called precancerous dermatosis, xeroderma pigmentosum, Paget's disease, leukoplakia and roentgen-ray keratoses themselves, will not be discussed.

DYSTROPHIES

Dystrophies may be atrophies or hypertrophies. Obviously, atrophies afford none of the conditions under which the roentgen rays could be efficacious. Hypertrophies, except those mechanically produced by irritation, also are no particularly fruitful field for roentgen-ray therapy. Icthyosis, keratosis of the hair follicles, possibly Darier's disease and acanthosis nigricans, do not seem to respond often to the roentgen rays. Occasional favorable reports creep into the literature, but in our experience only follicular keratoses seem at all amenable. Some inflammatory hypertrophies, not properly belonging to this group, and perhaps better regarded as hyperplasias, respond with a certain degree of uniformity to the roentgen rays. These are clavus and callus, including the plantar wart. In a preponderance of cases, from two to five irradiations of

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1 M (H s.d), at intervals of four weeks, will cause the lesions to disappear, if the underlying mechanical irritation is likewise removed.

FUNCTIONAL DISEASES: PRURITUS

Excessive function of skin glands is controllable by the roentgen rays under conditions mentioned in connection with acne. Hirsutes does not properly belong here, and the attempt to produce permanent alopecia by means of the roentgen rays is mentioned only to be condemned.

Pruritus, particularly of the vulva and anus, is amenable to small doses of the roentgen rays at frequent intervals, or larger doses at less frequent intervals, the maximum at each exposure, however, being one-half M (H s.d.). Three quarters of these cases can thus be cured, or at least relieved.

CONCLUSIONS

1. The therapeutic use of the roentgen rays covers a wide territory. All other methods of internal and external management should be pursued at the same time. What stands out most clearly is that voluminous infiltrations, whether neoplastic or inflammatory, and whether accompanied by epidermal changes or not, are most amenable. In addition to this, diseases depending on functional or productive overactivity, such as acne, are equally amenable. Further, the roentgen rays are of equal use in producing the mechanical removal of infected hair.

2. Neoplasms, including the noninfectious granulomas, are favorably affected through the influence of the rays on young, rapidly multiplying cells.

3. Acne is cured by an alteration of the skin through the inhibition of gland function, and of the reproductive ability of the follicular epidermis.

4. The infectious granulomas are cured partly through the mechanism outlined in connection with neoplasms, and possibly because the causative organisms themselves are slightly affected.

5. The simple inflammatory lesions are curable only when there is hyperplasia of the epidermis and a marked infiltration. The former is influenced by the inhibiting effect of the rays on the reproducing cells, and the latter by the destructive effect on the infiltrating cells,

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which are mainly of the lymphatic type, as well as on the reproducing fibroblasts.

6. Why the rays favorably influence pruritus is not known.

7. By understanding the type and volume of lesions and by realizing that conditions in themselves atrophic are unfavorable for roentgen-ray treatment, it can be determined, from an understanding of the simple histopathology of skin lesions, what the dose and what the intervals should be.

8. Without this knowledge, the use of roentgen rays is a purely arbitrary and mechanical procedure.

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CARCINOMA OF THE TONGUE AND ITS TREATMENT WITH RADIUM

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Cancer of the tongue is most often seen between the fourth and sixth decades and is much more common in men than in women. It occurs most frequently on the side of the tongue, but may occur any place. Pathologically, it is practically always of the squamous cell type of carcinoma. Among the etiologic factors, syphilis, and trauma produced by rough teeth and by the use of tobacco are of prime importance.

The variation in the reports of the frequency of syphilis in carcinoma of the tongue, (3.38 per cent., according to Meller, to 84.23 per cent., according to Fournier), is probably in proportion to the incidence of syphilis in the clinics from which the statistics are taken. It is certainly true that a syphilitic lesion may be a precancerous lesion. A gumma, leukoplakia, or chronic syphilitic glossitis may be the starting point of cancer, though the determining factor may be obscure. This determining factor is undoubtedly often a matter of time or of trauma, or of both. An untreated syphilitic lesion of the tongue should always be watched with suspicion, especially when subjected to the trauma of the excessive use of tobacco or of a rough tooth. In the nonsyphilitic patient, cancer may apparently be caused by the use of tobacco in any form. Also, in the nonsyphilitic, carcinoma may develop in a chronic ulcer caused by an untreated rough tooth. Nevertheless, cancer of the tongue does appear with startling frequency in nonsyphilitic nonsmokers, without the presence of a rough tooth. In addition to these factors, there is probably an inherent tendency toward cancer formation which is, after all, the chief factor. The recognition and proper treatment of syphilis of the mouth, and proper dentistry, will undoubtedly lessen the frequency of cancer of the tongue.

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Leukoplakia should be treated by stopping smoking, by specific treatment if indicated, and by the use of a mouth wash, such as sodium thiosulphate (hyposulphite). If these measures fail, radium should be applied. It is usually curative and is far more satisfactory than surgery or cauterization. The treatment of a chronic ulcer, due to a smoker's burn or the irritation of a ragged tooth, is the removal of the apparent cause, and, if this is not sufficient, surgery, cauterization with the actual cautery, electrocoagulation or the galvanic cautery, or radiation, should be invoked.

The diagnosis of carcinoma of the tongue is frequently difficult. It is often impossible to differentiate positively syphilis, tuberculous ulcer and carcinoma, clinically. As a rule, the syphilitic lesion is not so hard as carcinoma, develops more rapidly, and occurs most frequently on the dorsum of the tongue, while carcinoma is most common on the sides. These criteria are, however, not final. The blood Wasserman test should be made in every case and, though it is negative, a therapeutic test consisting of two or more arsphenamin injections should be given, if there is still some doubt. The Wassermann reaction here, as elsewhere, should be regarded as only one piece of evidence. Even the therapeutic test may be misinterpreted at first, because we often see syphilis and carcinoma in the same lesion, with the result that the lesion clears rapidly for a time under antisyphilitic medication, giving us a false sense of security. Tuberculous ulcers simulating broken down gummas, though rare, may be found on any portion of the tongue and are usually seen in persons with chronic tuberculosis. Although these tuberculous lesions are usually irregular, undermined and soft, it is occasionally impossible to make a positive clinical diagnosis, and a biopsy, as well as therapeutic tests, should be resorted to. There is still much controversy as to the danger of doing a biopsy, but probably little damage is done if the specimen is obtained from near the center of the lesion, with a minimum of trauma. The advantages of having made an absolutely positive diagnosis before instituting treatment of any kind are obvious.

The surgical treatment of carcinoma of the tongue has been the accepted form of therapy. As in surgical treatment of cancer elsewhere, it is necessary to remove the lesion with a very wide margin. Even in the earliest cases, the most conservative operation finding favor with the surgeons is hemisection. In the more extensive cases, complete

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amputation of the tongue is done, often with the removal of the floor of the mouth. These operations are not only terribly mutilating, but also carry with them a high mortality, even in the most skilled hands, and are productive of but few cures.

During the past few years, a number of physicians have treated cancer of the tongue by electric coagulation, usually in conjunction with radiotherapy. In capable hands, the results are frequently satisfactory.

The treatment of carcinoma of the tongue with radium has many advantages. In the first place, there is no primary mortality. In contrast to this, we see a primary mortality in the surgical treatment varying from 10 per cent. to 30 per cent., depending on the extent of the lesion. Secondary death, due to hemorrhage or infection, is far less common after radium than after surgery. A palliative result can be obtained in a majority of the cases with radium treatment; while, even if the patient survives the operative procedure, he is left with greatly impeded speech and is able to eat only with great difficulty and there is frequently increased rapidity of growth. It is not possible at this time to estimate the percentage of cures by radium, because the method has not been in use long enough and because the majority of the cases which we are now seeing are the ones that the surgeons consider hopeless. The percentage of cures for surgery is less than 20 per cent., even in picked cases. The great disadvantage of radium in these cases is the painful reaction. It is impossible to estimate the severity of this in advance. In some of our cases, the period of reaction was not long and the healing of the ulcer and softening of the lesion were prompt. In others, the amount of suffering was out of all proportion to the extent of the lesion and the clinical appearance of the reaction. We have not as yet been able to devise a satisfactory way of combating the reaction.

The ideal method of treating these cases is by the insertion of the tiny unscreened tubes of radium emanation. This method has been described and was first used by Janeway and Quick of the Memorial Hospital of New York City. At present, we feel that it is best to give the entire dose at one sitting and attempt to seed the entire indurated area with the tiny emanation tubes, each containing about 1 millicurie, inserting from five to ten or more tubes depending on the size of the lesion. This gives an even, intense radiation throughout the tumor mass. In inserting the tubes, we attempt to keep them within the carcinomatous tissue and do not intentionally place any of them in the

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surrounding normal tissues. In addition, we sometimes crossfire from the surface by using a radium plaque or an applicator of a number of tubes.

The reaction occurs a little earlier following the use of buried bare tubes of emanation than following the surface application of radium. It starts as a rule in about seven days, is usually at its height in from two to three weeks, and then gradually diminishes. This reaction consists of an increase in the swelling, with burning pain, and often an increase in the size of the lesion due to ulceration following the separation of the slough. A reaction on portions of the mouth adjacent to the area treated is a constant and often painful and unpleasant feature. In favorable cases, after the height of the reaction has been reached, the lesion softens rapidly and then heals slowly. Most of the patients complain of pain radiating to the ear. This is sometimes of long duration, frequently outlasting the period of visible reaction. Probably the next best method to that of burying bare tubes of emanation is the insertion of steel needles, containing radium element, into the tumor mass. The number of these and the time of exposure depend on the strength of the needles and the size of the lesion. This method probably causes more tissue destruction than does the bare tube method and does not give as intensive a local radiation. The use of surface applications of tubes or plaques alone is certainly the least satisfactory form of therapy and can be expected to give no more than palliative results, except in the most superficial cases.

At the same time that the tongue lesion is treated, the cervical glands should receive a massive dose of roentgen ray, covering three areas, the front and the two sides. If there are palpable glands that are clinically malignant, these should be removed about two weeks after radiation, if they are operable. If they do not appear to be operable, bare tubes may be buried in them at the time of a partial operation, or inserted through the skin under a local anesthetic. If no glands are palpable, the patient should receive two or three courses of roentgen-ray therapy and be kept under close observation for as long as possible. Should glands develop under treatment, they should be operated on at once, and the roentgen-ray treatment continued after operation. During operation, bare tubes can be buried in any suspicious place. The technic of the roentgen-ray treatment is constantly being changed. During the last year, we have increased the distance and the screening considerably, and

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we are apparently getting better results. We have practically entirely given up the use of the radium pack to the neck in these cases as uneconomical and no more effective than the roentgen ray. It is probable that the newer deep therapy machines will still further improve our results.

During the last two and a half years, we have treated fourteen patients with carcinoma of the tongue, including two that were first treated just prior to the installation of the emanation plant at the University of California Hospital. Two of the patients were women. The ages varied from 36 to 93 years. Four had syphilis in addition to carcinoma. Four are clinically free of the disease, two at two years after treatment, one at one and a half years and one at six months. Five showed cervical metastases at the time treatment was instituted and five of the others developed an involvement of the glands during treatment. None of these patients survived. Ten are dead, or when last seen were in such condition that the end was only a matter of time. Several other patients received their first treatment but did not again report for observation or further treatment, and were not traced. It is possible that all our patients clinically cured will not remain well, but we have the satisfaction of having prolonged life without mutilation. It is reasonable to expect that with improved technic it will be possible to cure 25 per cent. of unselected cases of carcinoma of the tongue by radiation.

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CANCER OF THE LIP TREATED BY ELECTRO-COAGULATION AND RADIATION

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In the latest stages of cancer of the lip, neither radiation, electrocoagulation, nor any other form of treatment can be expected to cure the patient. Therefore, to cure cancer of the lip, as in any other form of cancer, it should be treated early and thoroughly. Thorough treatment of cancer of the lip means radiation, no matter what other form of treatment may be used in combination. I believe that a patient suffering with cancer of the lip does not get all possible chances of recovery unless radiation is given. Whether radiation should be used alone or combined with other treatment is a matter of careful judgment in the individual case. As a prophylactic measure, every point of irritation affecting the lip should be removed, such as irritation from a pipe, cigaret paper, excessive cigar smoking, traumatism, irritation from a jagged tooth, or excessive exposure to heat, cold and wind. Any fissure or crust formation on the lip that lasts for four weeks without complete healing should be looked on with suspicion. Practically every one of these lesions, especially if there is associated any induration at the base, is potentially malignant, if not actually so, unless due to syphilis. If patients are thoroughly treated in these early stages, practically all should get well.

RESULTS OF TREATMENT

I will review only the cases treated in my private clinic, because of the difficulties in tracing the patients in the hospital clinics. Many patients have been treated in the roentgen-ray departments of the hospitals. Most of these were postoperative or recurrent cases, and, in many instances, the patients did not consider themselves our patients, or looked on the postoperative treatment as an unnecessary annoyance, and often prematurely discontinued treatment. The recurrent cases

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were generally far advanced, and were referred to the department because there was nothing else to do. They were usually hopeless cases.

The early cases will, of course, give the best results, and, if treated thoroughly, all patients should get well. My records do not show that all do get well, but in the cases in which we failed the patients were difficult to manage. One had an associated syphilitic infection. He developed an extension in the cheek and jaw after seven years, and died during this stage, from pneumonia. It was always doubtful whether this induration about the angle of the jaw, but above the lower edge of the bone, was syphilitic or malignant, and he would not permit a section to be removed for microscopic examination. In another case in which we failed, the patient did not return after the first treatment. The third failure, I believe was due to insufficient treatment at the very beginning. While there was no local recurrence, an indurated ridge developed at the inner border of the original lesion and extended downward and outward toward the right submaxillary gland. The side of the cheek from the angle of the mouth to the submaxillary gland became indurated and undoubtedly malignant. The patient became discouraged; but at the time of the last visit the submaxillary gland was not palpable. It seems that the treatment given to the submaxillary region was efficacious.

In another case, eighteen months after the primary lesion had disappeared a metastatic lymph node developed in the submaxillary region. In looking about for the cause of this surprising fact, we found that, through some mistake in the office, he had not received treatment over these areas. While it is unfortunate for the man, it illustrates beautifully the importance of thorough treatment of the lymphatic areas by radiation, either with the roentgen rays or radium, at the time of beginning treatment of the primary lesion, and subsequently sufficient to insure thorough destruction of the cancer cells. This recurrent lymphnode has since been treated, apparently with success, by the insertion of radium needles.

In my private clinic, we have treated 105 cases of cancer of the lip: primary eighty, recurrent twenty, postoperative five. In eighty primary cases from my private records, seventy-four patients recovered, and have remained well from several months to eighteen years. Two died of a continuation of the disease, two have had a recurrence and in two the result is unknown.

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I realize that such a record is not beyond criticism, because the duration of the results is variable, and other failures may have to be recorded. However, since the results obtained by my colleagues, Henry K. Pancoast and William L. Clark, correspond so closely to my own, and were obtained by similar technic, and since the results in the older cases are most satisfactory, I am led to believe that our enthusiasm is justified and that this method of treatment can be recommended.

The recurrent conditions are always more difficult to cure. In the twenty recurrent cases treated, only eight patients recovered. Much will depend on the promptness and thoroughness with which these patients are treated; but, in part at least, the results will depend on the nature of the cancer or the degree of malignancy. One must obtain prompt results from radiation or failure is likely to result. Thorough radiation by the roentgen rays, and by radium when it can be combined to advantage, from the very beginning is most important. I never like to have a patient referred to me after some one has used insufficient radiation over a considerable period of time, and then, having recognized failure, has concluded that perhaps more thorough radiation may produce good results. In such cases, unless the lesion is so situated that it can be destroyed by electrocoagulation, failure will be the rule.

The five patients given postoperative treatment have remained well, though in none was there a block dissection.

TECHNIC

In the treatment of malignant disease, probably more than in any other field, skill and keen judgment are required. One must understand the nature of the disease and its lines of distribution. One must then use enough radiation to destroy the cancer cells and at the same time do as little damage to healthy tissues as is possible. Boggs [1] says, "Too many failures have been accredited to radium, when, as a matter of fact, through inexperience and lack of proper study, only partial doses were given."

Electrocoagulation.—Electrocoagulation consists in the coagulation of the diseased areas by means of the heat produced by the high frequency current as it passes through the body from a point attached either to the Oudin current or to one pole of the d'Arsonval current.

1. Boggs, R. H.: Radium Treatment of Mouth and Throat, Pennsylvania M. J. **25**:22 (Oct.) 1921.

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The Oudin current (unipolar) is used for small lesions, and the d'Arsonval current is used for the larger lesions. If the d'Arsonval current is used, one pole is attached to a pad or smooth metal electrode placed under the buttocks of the patient, while the active electrode is a point. This current is not selective in its action, but will destroy the tissues radiating outward from the point. One cannot use this current, therefore, in locations in which essential structures, such as important blood vessels or nerves, are located in the line of destruction. There will be a zone beyond the actual coagulation which will be superheated and will be sufficient to destroy cancer cells, but will not destroy the healthy tissue. In this way, one conserves tissue; and, as is shown by my own cases and by those shown by Clark,[2] the defect after the patient is well does not nearly equal the amount of diseased tissue removed. There is, apparently, a regeneration of a part of the tissue removed. The heat is generated in the tissues. It is the penetrative value of this form of heat that makes it more desirable than that obtained by the thermocautery, which destroys only by transmitted heat and, therefore, is essentially more superficial. The destructive value of the current used can be learned only by experience, but experience can be obtained by practice with a piece of liver, or other meat. Such experience from practice with a piece of liver cannot be directly transferred, for the current value will vary with the shape of the lesion to be destroyed, whether small and prominent, such as a wart or mole, or flat and indefinitely outlined, as in carcinoma. The current value will also vary with the size of the mass or body to which the tissue to be destroyed is attached. The milliamperemeter is not of great value in judging the effects.

The tissue as it is destroyed by the high frequency current turns white, if it is coagulated; or is dried up, if small, and sparked through the air. (Desiccation.)

Selection of cases suitable for electrocoagulation is necessary. If the lesion is small, and its removal will not cause too serious a defect in the lip, I believe that such destruction will be followed by more prompt and more satisfactory results than by radiation alone. By such destruction, we macroscopically remove the diseased tissue just as the surgeon does with the knife, but we do it without opening any blood vessels

2. Clark, W. L.: Cancer of the Oral Cavity, Jaws and Throat, J. A. M. A. **26**:1365-1369 (Oct. 26) 1918.

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or lymph channels. If the lesion is fairly large, I trim the destroyed tissue away with curved scissors, always carefully cutting within the destroyed area. In this way, one eliminates part of the disagreeable odor which accompanies the sloughing process.

If the cancer involves the entire lip, or even half of the lip, such preliminary destruction by electrocoagulation is impractical, unless one can foresee some means of closing the mouth by a subsequent plastic operation. If such a subsequent plastic operation is planned, the surgeon who is to perform the operation should see the patient and be consulted in advance, before the radiologist attempts the destruction. We have no more right to assume in advance what the surgeon's judgment and procedure will be than the surgeon has a right to assume what the judgment and procedure of the radiologist will be. Both specialties are developing too rapidly for either to take up the other as a side issue, and more will be accomplished by cooperation.

Generally speaking, I believe that, in these advanced primary cases, a thorough trial should be made first with applications of radium, and if it is skilfully applied, good results may be expected. In some cases, marked temporary improvement only may occur, and a stage is then reached in which the disease is at a standstill or may begin to progress in spite of radiation. At this stage, complete and thorough local destruction or complete surgical excision is probably the only procedure left. With the cooperation of skilful surgeons, I have had success in some such advanced cases.

RADIATION

Radiation is indicated in all cancers of the lip, no matter what other treatment is used, and sufficient radiation must be used actually to destroy the cancer cells. If a patient is to be operated on surgically, a preliminary radiation with a full erythema dose should be given over the lip and chin, and in the submental and submaxillary regions; and, after the operation, and two to three weeks after the preliminary treatment, similar radiation should be given. The patient should then be kept under observation for several years, and more radiation should be applied if there is the slightest sign of recurrence. This same sort of radiation should be added to electrocoagulation, and can be applied most practically by means of the roentgen rays. For this purpose, I use a 9-inch spark gap, with five milliamperes of current, through 6 mm. of aluminum filter, at a distance of 30 cm. for twenty-five

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minutes. The time must be governed by the radiation value of the individual instrument used.

If one possesses sufficient radium and sufficient skill in its use, most and perhaps all local cancers of the lip can be cured by this means. It will require more time, more skill, more patience than by the combination of electrocoagulation and radiation, but there will be more preservation of tissue and a better cosmetic result than can be obtained by any combination with surgery or electrocoagulation. Therefore, I can lay down no rule for the treatment of all cases. The circumstances surrounding the individual case should govern our procedure.

If radium is to be used for the local destruction of the cancer with preservation of the tissue, the local tissues must be kept saturated to the limit of toleration of the normal structures until the cancer entirely disappears.

If one has sufficient radium, the submaxillary regions can be treated by surface applications, properly screened.

If metastatic nodules are palpable, they should have preliminary radiation as described, and should then be dissected out surgically, or treated by the insertion of radium needles sufficient to destroy the disease.

Radium needles of 10 mg. each may be inserted, 1 cm. apart, throughout the diseased area, and left in place for eight hours. Following the insertion of radium needles into tissues, there is the production of fibrous nodules, especially when the needles are placed farther apart, and left in place sixteen hours. These nodules are composed of fibrous tissue and result from the necroses produced by the radium. They will lead the untrained to suspect malignant nodules or redevelopment of the disease. With our meager knowledge on this point, it will require considerable skill to be able to distinguish between the disease and the fibrous tissue. Therefore, I urge close observation, lest a false security lead to neglect of true malignant disease.

CONCLUSIONS

1. Any fissure or crust on the lip which lasts over a month should lead to suspicion of malignancy.

2. Local destruction by electrocoagulation, followed by thorough radiation, should effect a cure in practically all cases if patients are treated early.

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3. Thorough radiation by radium or the roentgen rays should be given over the lymphatics draining the diseased area.

4. Recurrent carcinoma gives much less satisfactory results.

5. Metastatic lymph nodes should be treated by surface radiation and then by radium implantation or by excision.

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TREATMENT OF CANCER OF THE LIP BY RADIATION

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OKLAHOMA CITY

At the meeting of this Association in New Orleans, 1920, I presented a paper before this Section,[1] "A Clinical Study of Epithelioma of the Lower Lip," in which I considered more especially the pathologic anatomy and clinical classification of epithelioma of the lower lip, as observed and recorded in the private practice of my associate, Dr. M. M. Roland, and myself. In this paper, I mentioned only briefly the technic of treatment and results. Today, I am presenting to you briefly our technic of treatment by roentgen ray and radium of 248 consecutive cases of cancer of the lip which have occurred in our private practice from Jan. 1, 1909, to Dec. 31, 1921.

Tracing by letter of inquiry to family physician or patient, or by other methods, the present condition of each patient or the cause of death, and correlating the facts from such a number of patients with cancer of the lips who have been treated is no small undertaking, as those who have had experience will testify.

Also, I shall repeat these diagnoses have been made largely from a clinical rather than a biopsy examination. Judging from statistics from the Mayo Clinic, as given by Broders,[2] and from the laboratories of Bloodgood, as quoted by Hazen,[3] not less than 96 per cent. of our cases were of the prickle or of the squamous cell variety.

1. Lain, E. S.: A Clinical Study of Epithelioma of the Lower Lip, J. A. M. A. **75**:1052-1055 (Oct. 16) 1920.

2. Broders, A. C.: Basal Cell Epithelioma, 1912 Mayo Clinic Reprint, read before Southern Minnesota Medical Association, Mankato, Jan. 20, 1919.

3. Hazen, H. H.: Prickle Cell and Basal Cell Skin Cancers, J. A. M. A. **64**: 958 (March 20) 1915.

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This total does not include a smaller number of cases in which the patients have been treated by interns or nurses in the Oklahoma State University, and in other hospitals of our city in which our services were only of a supervisory nature. This review of patients treated includes a goodly number who were treated several years prior to that enduring work toward arithmetical computation of roentgen-ray technic which was done by MacKee,[4] Shearer and their co-workers. Also, much of our radium treatment covers a period antedating the more accurate methods of screening or filtering in order to get the effects of the more penetrating gamma rays.

Since about 1915, we have classified our patients into three groups, according to the location of the lesion upon the lip, and the degree of development, which to us also largely indicates the prognosis. This classification was presented in full in my former paper, and I shall repeat only briefly:

Group 1: Those lesions which are situated wholly on the cutaneous border of the lip, are not deeply indurated and are without palpable or other evidence of metastasis in adjacent glands.

Group 2: Those in which the lesion most commonly also overlaps the mucosa of the lip and are deeply indurated, and in which the adjacent submental or submaxillary glands are palpable. This group also includes a few cases of recurrences from former attempts at a cure by caustic applications or unsuccessful surgery.

Group 3: Those of obvious metastasis in more than immediately adjacent glands. Approximately, this entire group is composed of patients who have previously tried repeatedly some other methods of treatment and whose conditions are now hopeless so far as a final cure is concerned.

Medical literature on radiotherapy of cancer is becoming so voluminous and laboratory examination of radiated tissue has so frequently verified the following statements that they have become axioms to the experienced radiotherapist and are no longer debatable.

1. Immature and rapidly growing cells are more sensitive to radiations than those which have acquired their adult physiologic character. This is known as the law of Bergonie and Tribondeau. This change

4. MacKee, G. M.: X-Ray and Radium in the Treatment of Diseases of the Skin, Philadelphia, Lea & Febiger, 1921, p. 134.

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is more noticeable after radiations from the hard beta or the gamma rays of radium than after hard roentgen rays.

2. The most susceptible period in the life of this cell is the time of its division, when its nuclear life appears more amenable and accessable to this energy.

3. All types or characters of cells are not equally affected by the same degree or length of radiation, squamous or prickle cells and certain types of connective tissue cells requiring the greatest, basal lymphoidal and endothelic the least.

4. The lethal dose for a certain type of cell, such as the basal, may be only sufficient to stimulate to a more rapid growth a squamous or a connective tissue cell.

5. The shorter the waves of energy given off from radium or a roentgen-ray tube, the more penetrating and therefore the more effective are they in the disintegration of the cancer cell.

The more recent conjoined study of the physicist and radiotherapist has given to us a more accurate and scientific method of screening the rays so that roentgen rays and radium are now achieving cures in many cases of cancer formerly classified as inoperable or hopeless.

In the treatment of our cases, we have followed no invariable routine, except as regards certain proved or unquestioned procedures. One of the latter is the radiation of the submental and submaxillary glands by hard or gamma rays in all our cases of cancer of the lower lip.

The treatment of metastasizing areas has, in most cases, been given by roentgen ray, using M. A. of from 3 to 5, spark gap of from 6 to 10 inches (15 to 25 cm.), anode distance of from 8 to 18 inches (20 to 45 cm.) with filters from 1 to 4 mm. of aluminum. Later, we added from 0.25 to 0.5 mm. of copper, giving a time of twenty minutes to one hour each position. During the past two or three years, we have been giving a dosage to glands, expressed in modern terms, a K.V. 100, M.A. 5, focal distance from 16 to 18 inches (40 to 45 cm.), time from twenty-five to forty-five minutes, repeated as indicated in six weeks.

This variation in technic does not appear so inconsistent when I explain that our evolution in treatment has consisted of an increasing potentiality over a period of fourteen years. Considering the cycle-like development of the pathologic cells, and reviewing our total treatments

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as well as the opinions and statistics of others, we are fully convinced that two or three properly timed and filtered doses of radium applied within intervals of a few days are more destructive to any type of cancer cell than the total given at a single exposure. The so-called fractional dosage, with either roentgen ray or radium, is much to be feared, although it is more successful if a nearly lethal instead of a stimulating dose for the pathologic cell has each time been given.

Perhaps all radium specialists may not agree with our conclusions; still we have by experience been fully convinced that the destruction of a certain class of early and externally located basal cell cancers on the lips or elsewhere on the body may be more rapidly accomplished, and without an objectionable scar, by the use of the combined hard beta and gamma rays than by the gamma rays alone.

In a certain type of case under Group 1, in which there is a proliferating keratotic elevation with only a mild degree of infiltration, it has been our custom, first, to apply a 10 or 20 mg. plaque, screened with 0.10 mm. of aluminum for a period of two or three hours. This will cause, after ten or fifteen days, a reaction, which is followed, after twenty or thirty days, by degeneration and perhaps an exfoliation of all superficial pathologic cells.

Before this reaction has begun or immediately after the first application, we apply a plaque of from 10 to 20 mg., with screening of 0.3 mm. of brass, for eight to twelve hours. This filter permits only about 5 per cent. of the hardest beta rays and yet utilizes all the gamma rays for deeper effects. Thus we produce, in from four to six weeks, a perceptible softening and perhaps a complete disintegration of deeper cellular structures of cancerous nature.

In the treatment of Class 2, lesions of deeper and more extensive development, or of the squamous or the prickle cell variety, we first apply a 10 or 20 mg. plaque of radium over the lesion, screened with 0.3 mm. of brass for from ten to fourteen hours, reinforced within a few days by a pack of from 100 to 160 mg. of radium screened with 2 mm. of brass and placed on a pad of gauze of from 1 to 3 cm. in thickness. This pack is located over regions of possible metastasis for a total of from fifteen to twenty hours and this application may be repeated within a few days until a total of from 2,000 to 3,000 mg. hours have been given.

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In a certain class of indurated or deeply nodular cancers of the lips, we follow the applications of the plaques with as many radium needles inserted from 1 to 4 cm. apart as are necessary thoroughly to radiate the entire area of the cancerous growth. These are left for from three to five hours. Inserting the needles causes no severe pain if the entire growth is first injected with a 1 per cent. solution of procain.

We are indebted to Drs. Boggs, Clark, Pfahler and others for calling our attention to this valuable advancement in the application of radium to this class of cancers.

In tabulating our total number of cases of cancer of the lips, I wish to call attention to the following interesting findings:

Twenty-seven patients were examined and, after having the method of treatment explained and prognosis given, refused treatment.

In eight cases, or about 3.2 per cent., the lesions were located on the upper lip. Two of these patients were females.

In nine of the total number of cases of cancer of the lip the patients were females, and five of these were users of tobacco. Of Class 3, only three are now living and each still shows evidence of progressive cancer.

Each of the eight cases of Class 3 and ten cases under Class 2 were recurrences following caustics or surgery. Of eight deaths under Class 2, five followed the employment of caustics and three were post-operative cases.

If we eliminate from Class 1 one patient who died from a cancer on the hand, one who died from a sarcoma at the point of the shoulder and one who died from generalized lymphosarcoma, conditions which could scarcely be classed as metastases from the lips, our percentage of cures in Class 1 is 98 plus.

Under Class 2, we note that, since the beginning of the more recent and much improved methods of radiation with a heavy kilo-voltage and radium packs, or, better still, when radium needles are inserted into the glandular metastasis, our percentage of cures promises to fall not far short of that of Class 1.

CONCLUSIONS

The cellular morphology of a cancer of the lip has less importance in the prognosis than the location or degree of development, or the

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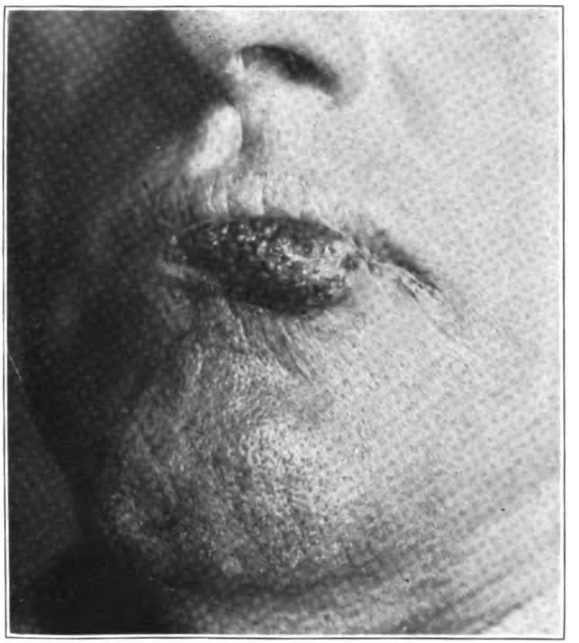

Fig. 1 (Class 1).—Cancer of lip.

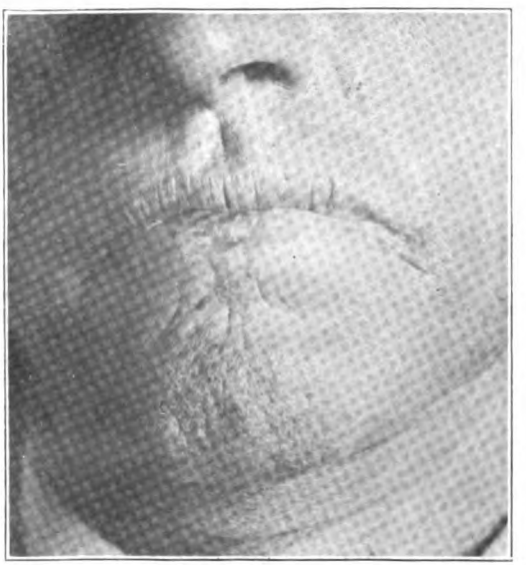

Fig. 2 (Class 1).—Patient shown in Figure 1, three years later.

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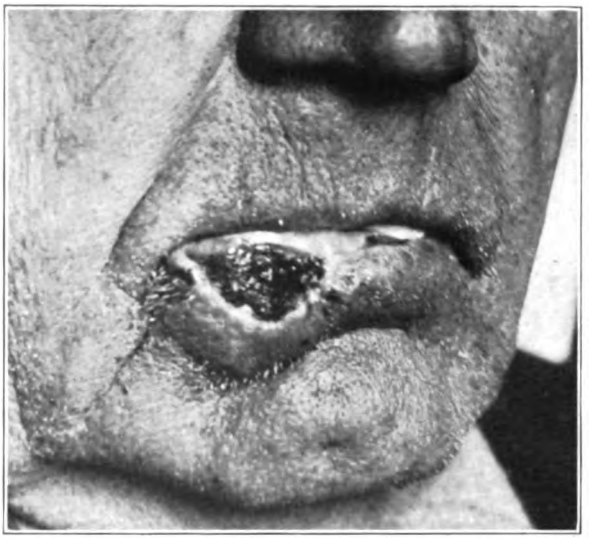

Fig. 3 (Class 2).—Cancer of lip, deeply infiltrated, involving submental glands.

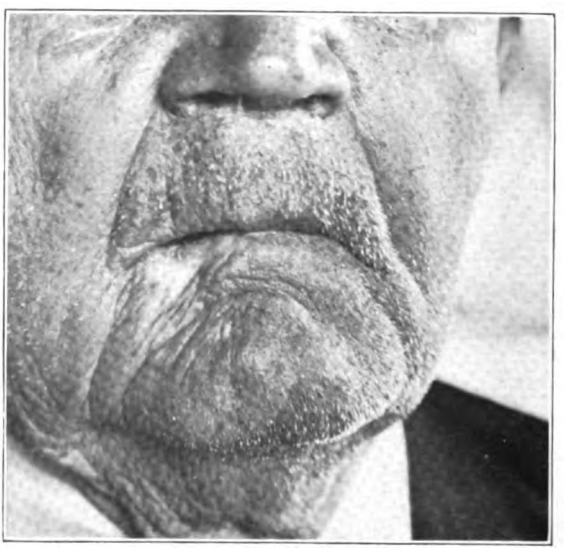

Fig. 4 (Class 2).—Patient shown in Figure 3; no evidence of recurrence three years later.

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age of the patient. We have repeatedly observed that, on account of a beginning atrophy of the lymph system, after a certain age the prognosis is better. Especially is this true in cancer of the lower lip.

TWO HUNDRED AND FORTY-EIGHT CONSECUTIVE CASES OF CANCER OF THE LIPS

Treatment and Results	Number	Percentage
Refused treatment	27	
Total taking one treatment only for palliative purposes or taking up some other form of treatment	13	
Total number of cases of upper lip involvement: Class 3, two patients, both now dead; Class 2, one living; Class 1, six, all living	8	
Class 3 (all postoperative or postcaustic treatment), total number of cases—each traced	8	
Total number of patients living more than one year, one; two years, much improved, though not well	3	
Class 2: Total number of patients treated (seven cases were postoperative or postcaustic)	35	
Unable to trace	3	
Patients living and well after one year	32	
Well after three years, 18 patients treated	13	72.2
Living and well more than five years, 14 treated; two died from other causes	12	
Class 1: Total number of patients treated to January, 1922	156	
Died of accident, two: committed suicide, one, each during first year	3	
Died of cancer during first three years, one of liver, one of deep cervicals, one of generalized lymphosarcoma and one of cancer on back of hand	4	
Total living after one year	101	
Total number of patients treated more than three years	89	
Total living, no recurrence	87	97.7

We believe that a prickle or a squamous cell cancer, in the early stage of its growth, will undergo degenerative changes under radiations from either radium or roentgen ray just as the basal cell variety does. They differ only in the amount of radiation necessary and the technic of its application.

Finally, we believe that sufficient statistics verified both by clinical and by laboratory findings have now accumulated to justify the conclusion that cancer of the lip is equally and perhaps more amenable to treatment by roentgen ray or radium than by surgery, and in most cases radiotherapy is to be preferred.

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ABSTRACT OF DISCUSSION

ON PAPERS OF DRS. PARKHURST, HIGHMAN, TAUSSIG, PFAHLER AND LAIN

Dr. Gordon B. New, Rochester, Minn.: I do not believe any one is more enthusiastic about the use of radium in malignant disease of the head and neck than I am, but I believe that a great deal of harm has been done both to radium therapy and to patients when surgical conditions are treated with radium alone. I also believe that the good end-results of the treatment of epitheliomas of the lower lip with radium alone have been much overshadowed by the bad results. One must appreciate the fact that the diagnosis of these conditions must often be made microscopically. Fifty per cent. of questionable lesions of the lip are not malignant and must be excised for a microscopic diagnosis, so that the question of diagnosis must be considered in the cases of patients who are treated and cured with radium alone. If all lesions of the lower lip were excised for diagnosis, the mortality of epithelioma of the lip would be reduced a great deal; and I believe the cosmetic results in the cases I have seen treated surgically compare favorably with the results following radium. The glands of the neck should be removed in all cases of cancer of the lip. Radium should be given before and after operation, but not used alone in these conditions.

Dr. Joseph C. Bloodgood, Baltimore: The view I desire to emphasize is that at the present time the chief hope of preventing cancer is to get early cases, and I have demonstrated that 50 per cent. of the cases from which I have excised a V-shaped piece from the lip are not cancer. Another thing we must bear in mind is this: some people with cancer, who, before the days of publicity, waited so that we never saw them until they had hopeless metastases, now come to the physician early. Publicity has done that. We must also know what condition we are treating. We cannot make progress if we do not. Fifty per cent. of my last 100 cases clinically called cancer were not cancer. We have reduced the cases of cancer from 85 to 70 per cent. by excluding conditions that are not cancer; you cannot exclude cancer by reading the pathologic report. I want the sections and want them studied and restudied. The medical schools of the country have not the money to give us to make these investigations.

Dr. F. J. Eichenlaub, Washington, D. C.: Apparently dermatoses seen in the Middle West differ from those we see in Washington. I learn that ringworm of the scalp is cured by the application of a simple ointment, and now I learn that probably 98 per cent. of the cases of prickle cell cancer can be cured with radiotherapy. Our number of cases is small because we believe that prickle cell cancer of the lip is best treated with surgery, and so we send the patients to the surgeon. Of the fifteen patients we have treated, eight are dead or have recurrences; of the remaining seven, four have been well for only a year or two, so it is too early to call them cured. We have had one case treated just as a wart, then as a basal cell cancer, to the point of a third degree radiodermatitis. Before this reaction healed, the cancer recurred

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in the middle of the burn. When excised it proved to be a prickle cell cancer. This one case is enough to show that all prickle cell cancers cannot be destroyed by radiation, even when superficial and treated early. I cannot help but feel that surgery offers the best hope in prickle cell cancer of the lower lip.

Dr. William H. Guy, Pittsburgh: There seems to be a complete agreement in regard to prevention of malignancy about the tongue and lip by propaganda and publicity, and certainly we are all indebted to Dr. Bloodgood, if to any one, for what he has done to encourage this work. Further, there can be no divergence of opinion regarding the necessity for removal of points of irritation, and, in general, the application of oral hygiene, thus preventing malignancy in early cases that are definitely benign. There is a wide divergence of opinion, however, as to what is to be done after it is eventually determined that we are dealing with malignancy. Dr. Bloodgood's results are excellent, but I am not convinced that they are better than those obtained by other methods. We cannot attack every case in the same way and obtain the best results. Each and every case must be treated according to its own individual requirements. It would appear that in the early type of case classified as "local, likely malignant," without gland involvement, that either with surgery, electrocoagulation, or radium practically 100 per cent. are cured. In cases with gland involvement we find an increasing discrepancy of opinion. We have been told that nothing but excision of the mass with wide excision of the glands in the area will do. The difficulties of such a procedure are seen when we review the gland drainage of the area. All metastatic glands are not palpable, as we know, and many palpable glands are not carcinomatous, but inflammatory. A combination of methods, surgery, electrocoagulation and radiotherapy may be required in such a case. If absolute diagnoses are necessary, I favor biopsy, and this should always be preceded by the application of a heavy dosage of roentgen rays or radium. If these elements devitalize pathologic cells, radiation preliminary to either radical removal or biopsy is definitely indicated. There is still room for an honest difference of opinion in these cases. I am convinced that by a combination of methods and especially by the hypodermic method of using radium in both the primary growth and palpable glands, followed by intensive raying of the entire gland-bearing area, results at least equivalent to those obtained by advance surgery may be attained.

Dr. Richard L. Sutton, Kansas City, Mo.: I was much interested in Dr. Bloodgood's suggestion regarding tobacco as a causative agent in cancer of the mouth. In the Middle West, sunburn probably plays a more important part than tobacco. We see many cases of lip involvement. Seborrheic keratosis of the keratoid type not infrequently is followed by the development of carcinoma, usually of the prickle cell type. The fact that primary lesions are much easier to cure than secondary ones was first pointed out, I believe, by the late Dr. Heidingsfeld of Cincinnati. In those cases in which carcinoma recurs in scar tissue, one gets into all sorts of trouble. This is especially true in those cases in which caustics (such as arsenic paste, and similar

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agents) have been used. A cancer quack can take a simple, uncomplicated case of basal cell cancer of the skin, a case that could be cleaned up in a short time with radium, or even with a curet and acid nitrate of mercury, and by the use of some "simple, farm remedy," convert it into a lesion which involves not only the underlying periosteum, but the bone as well; and the patient is promptly placed beyond the possibility of a permanent cure. Dr. Elmer Twyman of Kansas City has called attention to the fact that as a rule in carcinoma of the lip the lesion exhibits a tendency to travel laterally downward, instead of directly downward. In my work with him, we have found best a combination of methods, radium and cautery for the mouth and tongue lesions, with erythema doses of roentgen ray in the submaxillary and submental localities. Carcinoma of the lower lip so often develops from keratoses. Only an eagle-eyed genius can know when all of the keratosis has been included in the excised area, and if it has not been, recurrence is prompt, and extension rapid, along the line of the scar.

Dr. G. A. Wyeth, New York: Dr. Taussig said that he has prolonged life in cases of carcinoma of the tongue without mutilation, and he consoles himself with this although he says he has had only a fair number of recovered patients. I think if he had mutilated a little more at the start he would have prolonged more lives and prolonged life longer. As Dr. Taussig said, many men have reported excellent results with electrocoagulation in the treatment of carcinoma of the tongue. It is not hard to understand how these excellent results have been obtained. The use of heat in the tissues from within, or endothermy, as I like to call it, greatly reduces the danger of metastasis and the likelihood of recurrence. How? Before a malignant area is touched it is completely surrounded by a wall of coagulation necrosis which destroys or seals off the blood vessels and lymphatics to and from the part. A specimen for microscopic section can now be taken with impunity, after which the whole malignant area is coagulated in situ and then cut out with scissors as an inert, necrotic mass rather than as a group of viable cells. Endothermy comprises two different technics, as developed by Dr. Clark of Philadelphia—desiccation for lighter work, coagulation for heavier work—and through them the operator has a wide range of destruction at his command. This is my reason for thinking we have fewer recurrences than surgery unattended has.

Dr. C. H. Ball, Tulsa, Okla.: If 50 per cent. of cases are not cancer, why perform a mutilating operation? If the condition can be eradicated by radium or roentgen ray, why not try that first instead of mutilating the patient? In my experience with the roentgen ray, results have been the same as Dr. Lain's. The roentgen ray removes the cancer and effects a cure in 98 per cent. of the cases. Why, if you obtain 98 per cent. cures, should you resort to any other method? Traumatic interference breaks down the natural resistance of the body, and metastases occur much sooner.

Dr. T. C. Kennedy, Indianapolis: I cannot agree with Dr. Bloodgood about his cures by surgery. If that is true, we have poor surgeons in the West. During the last year I have had nine patients come to me for radiation who

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had been operated within a year or a year and a half. He is certainly doing better work than our surgeons in Indiana. I have had many cases of carcinoma of the lip in the last few years and our results have been uniformly good. I do not mean that we cure all cases, for no method will do that; but in the treatment of cancer of the lip our results are so successful that I believe every patient should be treated with radium before operation is resorted to. If you treat the patient for a few weeks and the condition does not yield, it is not too late for operation. I think in every case the roentgen ray should be used before operation is advised. I do not know whether I understood Dr. New correctly, but I think he said he preferred operation. The cosmetic results from radium are far superior to any surgical results, and if we can cure these patients in this way, why operate? If there are any cancer cells, we are far more likely to spread them by operating than we are to cure them. I am satisfied that in cancer of the lip radium is more successful than surgical treatment.

Dr. F. W. Cregor, Indianapolis: I think we have no right to call these cases cancer until they have been proved to be cancer. Fifty per cent. of Dr. Bloodgood's cases called clinically cancer were proved not to be cancer. I do not think we should attack his position. I can subscribe to the position of Dr. Guy and of Dr. New, and I can also visualize an injury to normal tissue cells about these growths as the result of intensive roentgen ray or radium therapy. It seems to me like sending an army of cripples out to perform the functions of able-bodied men. According to Kinlock, the roentgen-ray burns that do not heal within a year become carcinomatous because of the traumatism of the normal tissue cells by the roentgen ray; so that if we are attempting to destroy these cancer cells which possess a very high radiosensibility, we must realize that we are injuring tissue cells that possess a lesser degree of sensibility, even though we are not destroying the cancer cells as we hope to do.

Therefore, I believe that the agent that destroys the macroscopically pathologic tissue, and the employment of radium, or especially roentgen rays, in the surrounding tissues afterward, in a dosage of not sufficient strength to impair normal tissue, but which we may hope will destroy pathologic tissue, is the method of choice.

Dr. John H. King, Nashville, Tenn.: Every case is a law unto itself, and we cannot use the same treatment in all. If we are treating a lesion on the lip, we should know the type of cancer and determine whether we are going to treat it with the roentgen ray, radium or electrocoagulation. If a case is treated by radium, the glands of the neck, submaxillary and submental, should receive deep roentgen-ray treatment or blunt dissection. I do not think we have a right to dismiss a patient without giving him the advantage of those two procedures. We know that many cases will recur, and we cannot say which they will be; if it is in our power to prevent these recurrences I think we should do so. Therefore, we should have a blunt dissection, a careful one, and a thorough radiologic treatment. A few weeks ago I had a case of recurrence in the submaxillary gland, that was quite large. I used the needle and

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heavy roentgen ray. The tumor-like formation disappeared remarkably quickly after three weeks. As the submaxillary and submental glands are the ones we first see affected, why can we not insert our radium needles in the areas we cannot strike with the rays? We cannot strike these glands because we cannot see them, but why cannot we do this as a prophylactic measure? It causes little discomfort, and we can leave them in for three, four or six hours as a prophylactic measure before any enlargement is observed.

Dr. Moses Scholtz, Los Angeles: One of the essayists has discussed roentgen-ray therapeutics in chronic nonmalignant inflammatory dermatoses, such as acne, lichens, psoriasis, eczemas, etc. There seem to be two points of view. The roentgen-ray experts and advocates of massive doses are looking for the largest dose that will not produce unpleasant after-effects. Another thing is to look for a minimum dose that will give the desired results. I think dermatologists should adopt the second point of view. There are essentially two dermatologic conditions calling for massive doses: malignancy and tinea of the scalp. In chronic inflammatory dermatoses we will get along much better with small fractional doses. I believe that in this group of dermatoses it is not only permissible, but distinctly helpful, to combine small fractional roentgen-ray treatments with exposures to ultraviolet light. By this means of additional sensitization we are able not only to reduce the number of roentgen-ray treatments to a minimum, but also the size of individual doses. I seldom use more than one-eighth or one-seventh of a skin unit with a spark gap of from 4 to 6 inches in chronic eczemas, lichens, acnes, etc. I cannot see the advisability of using one-fourth of a skin unit for many weeks in acne, a condition so benign and yielding so readily to therapeutics. Only very few, truly exceptional, cases would justify such heroic treatment. An overwhelming majority of acne cases will yield to ultraviolet light alternating with casual roentgen-ray treatments of much smaller aggregate dosage.

Dr. I. L. McGlasson, San Antonio, Texas: I take it from Dr. Bloodgood's and Dr. New's remarks that they meant the best type of surgery and perhaps compare it with ordinary radiotherapy. Then the results are not 100 per cent. perfect. All surgeons are not the best surgeons, nor are all radiotherapists the best in their line. All these things should be taken into consideration in discussing this subject in an effort to arrive at a conclusion. Dr. Bloodgood's statement is broad even for so eminent an authority. I am satisfied with my present treatment of cancer of the lip. I think I have overlooked something good in not following Dr. Pfahler's method of electrocoagulation, and I think that his plan is well worth while. Many patients with recurrence of cancer of the lip are sent to us by surgeons, and in these cases we get the worst results. If we have a failure, they say that radium is no good. I am curious to know whether the friends who talk against radium actually use it and have a sufficient amount. I think we should report our end-results, good or bad, until we can show something definite.

Dr. Davis W. Goldstein, Fort Smith, Ark.: I do not believe that in cases of cancer of the lip there can be any routine treatment. If we see a patient

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who has received no previous treatment, we believe that patient should receive radiotherapy. It does not make any difference whether you use radium, the roentgen ray or electrocoagulation to destroy the tumor. We formerly used carbon dioxid snow for the local lesion, with good results. Whatever method is used, the glands should be irradiated. If the patient has received previous treatment, I believe it is a surgical case. The cell is weakened by previous treatment, and it will not regenerate. I have had numbers of failures after the lesions were treated with caustics. The mucous membrane of the oral cavity is the most resistant of all tissues of the body to radium, and whether you use surgery, caustics or what-not, it is essential to take care of the lymphatics either by radium, roentgen-ray or complete block dissection.

Dr. Earl D. Crutchfield, Galveston, Texas: Some years ago I made a study similar to Dr. Parkhurst's. It seems to me that the reaction in these cases is more a reaction of the cell to particular environment under which the attack occurs than a definite specific reaction to the basal cell or the prickle cell epithelioma. Drs. Highman and Rulison spoke of the stimulating roentgen-ray dosage. In an incomplete study during the last eighteen months I have not been able to see any evidence of stimulation in any form of roentgen-ray dosage. I am not sure that the roentgen ray ever stimulates. The stimulation or reaction which may occur can be explained as a biologic reaction of the normal cells rather than as a stimulating reaction to the roentgen ray. In no case have I been able to see that mitoses were produced by the roentgen ray. One point in regard to surgery of the lip: Two or three years ago I studied serially sections of tumors of the lip which had been excised. Apparently on first examination many of these tumors seem to be small, localized lesions, but if serial sections are made, very often one is able to find small scattered cell nests in the edges of the lesions. The question then arises, When may we completely remove a lesion? If we knew that, then, perhaps, surgery would be the method of choice, for a great plastic surgeon; but if a piece of the lip is excised no man has the judgment to say whether or not the excision has been sufficiently extensive. We know that if ever a malignant growth is cut through, the possibility of metastases becomes very great. Therefore, since irradiation by the roentgen ray shows such a large percentage of cures radiation is certainly the method of cure; and electrocoagulation, which seals off everything, should be used as the method of removal.

Dr. Ben R. Kirkendall, Columbus, Ohio: I am glad that Dr. Pfahler has told us what to do for cancers of the lip that have been treated with roentgen rays but not cured. If we can cure these cases with electrocoagulation and not make them worse, it is a new method that can help us out. I think a great many nonmalignant growths of the lip would become cancers eventually. They are probably precancerous lesions, and the results we obtain with radium and the roentgen ray seem to be almost perfect in these cases. Dr. Lain's paper, with its statistics, shows almost perfect results with radiation, so why perform a mutilating operation first. That should not be resorted to until it is necessary. I believe that these patients, whether treated by radiation or surgery,

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should all be irradiated under the jaw where glandular involvement may occur. I wish to caution about the application of radium after roentgen-ray treatment in cases of cancer of the lip. I have had several cases of cancer of the lip in which the patients have first been treated, I suppose, with massive doses of roentgen ray. When they came to me there was probably more radiation in the growth than could be determined. We have been told not to treat with radium or roentgen ray until from four to six weeks have elapsed since the previous treatment. I have waited as long as four months to apply radium following roentgen ray and have had the whole lip slough off in two cases. Dr. Pfahler's electrocoagulation might have taken care of these patients and prevented this mutilation.

Dr. H. J. Parkhurst, Toledo, Ohio: There is at least one difficulty attending the use of arsphenamin as a therapeutic test in differentiating between epithelioma and syphilis: the arsenical preparations often seem to accelerate the development of a malignant process when it is present. Therefore, great caution is necessary. Concerning the subject of the tissue reaction in malignant epitheliomas, the literature contains few references; and this work has been offered with the hope of stimulating investigation along this line.

Dr. R. H. Rulison, New York: Dr. Scholtz says he combines the roentgen ray with the ultraviolet light. I have had no experience with this. In general, perhaps, we are too conservative, but if we have an erythema, due, possibly, to a simple sunburn, we are likely to postpone treatment and wait for it to subside, and on that basis I think we would not care to combine the two methods. Dr. Crutchfield makes the criticism that in one place we speak of the stimulating effect of the roentgen ray. Whether there is such an effect, I do not know. I have no defense to offer for using it, except that there are certain authorities who think this may happen. It seems to me we are not accomplishing much in the discussion because of the difference in terms.

Dr. Laurence Taussig, San Francisco: As I have tried to point out, the diagnosis of carcinoma of the tongue is difficult to make in many instances. Dr. Parkhurst pointed out the possibility of stimulating the growth by arsphenamin but, having made up our minds as to the probable diagnosis, we must treat it with that diagnosis in mind, being ready to change our method of attack whenever indicated. I think the main thing in carcinoma of the tongue is to make a correct diagnosis as early as possible in order to institute proper treatment.

Dr. George E. Pfahler, Philadelphia: We should treat each patient as an individual, and adopt the best treatment for each individual case. I have seen recurrences follow operations by the best surgeons in the country, whose names if mentioned would produce no doubt of their ability or good judgment. It must not be forgotten that the purchase of an amount of radium, either large or small, is no more a certainty of efficiency in its use than the purchase of a set of surgical instruments will guarantee a good operation. In my treatment with electrocoagulation, I always outline the surrounding edge in each

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case so that I know just how much is going to be taken away. That also seals off the lymphatics and blood vessels. I then trim it off with a pair of scissors, and at times the upper portion of that lesion can be sent to the pathologist for examination. There is no bleeding, which proves that I have actually sealed off the blood vessels and lymphatics. I give radiation over the lip and chin and the submaxillary and submental areas. This should be added to any other form of treatment. When there are palpable lymphatic glands, I am not sure whether these had better be treated first by general radiation and then excised, or whether we had better treat with general radiation and then introduce radium needles into the lymph nodes. I think we must let time tell us which is best.

Dr. E. S. Lain, Oklahoma City: Dr. King has asked me what I think of the treatment with radium needles introduced into all metastasizing glands or where metastasis might occur. I think this is good procedure though not as a routine treatment. This was done in one of our cases. As regards the standardization of roentgen-ray and radium treatments, I do not think such treatment can be standardized. Surgical or medical treatments are not standardized for any disease. If we should reach such a period, progress in therapy will cease. One thing that Dr. McGlasson mentioned I have also found true. Namely, in my Group 3, the advanced cases, all patients had previously been treated by plasters or by incomplete surgery. The radiotherapist has too long been made a "dumping ground" for hopeless cases, as has been said. You recall that twenty-seven of my patients did not take treatment, and that was largely due to our resolve not to be made a dumping ground for all cases in which other forms of treatment had failed. As regards the claim of a cure in 98 per cent. of squamous or prickle cell malignancies, Dr. Pfahler misunderstood me. I said that Hazen, quoting from the Bloodgood laboratory, reported that most cancers of the lips were of the squamous or prickle cell variety. I said that we have been able to effect a cure in 97.7 per cent. in Class 1. In Class 2, in which the glands were freely palpable and in which we had other evidence of metastasis, we have a percentage of 72.2 per cent. of apparent cures after three years. Our methods have improved during recent years, though had we combined other methods, such as Dr. Pfahler's electrocoagulation method, other patients might have been cured. Let me repeat that I do not believe we should entirely exclude surgery in the treatment of cancer of the lips. I do, however, insist that when we consider all phases of the patient's welfare and compare statistics on the various methods of treatment, we shall find in the use of radium and roentgen ray the most acceptable method.

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LIST OF FELLOWS OF THE AMERICAN MEDICAL ASSOCIATION REGISTERED IN THE SECTION ON DERMATOLOGY AND SYPHILOLOGY

List of Fellows of the American Medical Association who registered in this Section at one or more of the last five Annual Sessions, together with Fellows who are subscribers for the Transactions of the Section for 1922. The figures following the names indicate the record of attendance at the Annual Sessions (2 indicates 1922, 1 indicates 1921, etc.). T follows names of nonattendant Fellows subscribing for the Transactions for 1922.

Corrections will be appreciated.

Abbey, Frank L., Axtell Hosp., Newton, Kan., 2.
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Abernethy, Claude O., City Natl. Bank Bldg., Raleigh, N. C., T.
Alderson, H. E., 240 Stockton St., San Francisco, T.
Allison, Blake S., Madison, S. D., 2.
Anderson, H. V., Westfield, Ill., 2.
Angle, E. J., Funke Bldg., Lincoln, Neb., 8.
Auner, Jay F., Hippe-Polk Bldg., Des Moines, Ia., 8.
Ayres, Samuel, Jr., 50 E. 55th Terrace, Los Angeles, 2.
Ball, Charles Homer, Daniel Blk., Tulsa, Okla., 0, 2.
Baskin, Chas. L., 97 Borton Ave., Akron, Ohio, 2.
Bathurst, Wm. R., State Bk. Bldg., Little Rock, Ark., 9, 3, 4, 6, 7, 8, 2.
Beeson, Benjamin B., 7 W. Madison St., Chicago, 8, 0.
Belcher, Aubry C., Lewis Arcade Bldg., Huntington, W. Va., T.
Bernauer, Emil C., 82 Hancock St., Brooklyn, 7, 9.
Biddle, Andrew P., David Whitney Bldg., Detroit, T.
Bierhoff, F., 155 W. 58th St., New York, T.
Blaisdell, J. Harper, 45 Bay State Rd., Boston, 7, 8, 9.
Blickhan, A. J., 133 35 N. 6th Ave., Quincy, Ill., 9.
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Boardman, William P., 388 Marlborough St., Boston, 1.
Bradley, Mark S., 36 Pearl St., Hartford, Conn., T.
Brockelmann, Erich, 955 Hamilton Ave., St. Louis, 2.
Broeman, Clarence J., 4 W. 7th St., Cincinnati, 2.
Brown, Warren, Equitable Bldg., Tacoma, 1.
Brownson, W. C., Medical Bldg., Asheville, N. C., 4, 7, 1.
Bulkley, L. D., 10 E. 61st St., New York City, 2, 3, 4, 6, 7, 9, 3, 4, 5, 6, 7, 9.
Bull, Thomas M., 293 Church St., Naugatuck, Conn., 7, 9, 1.
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Butler, George Edward, 674 S. Main St., Fall River, Mass., 1.
Byrnes, Harry F., 67 Chestnut St., Springfield, Mass., 1.
Calvin, Warren D., Fort Wayne, Ind., 9, 0.
Campbell, R. R., 537 N. Normandie Ave., Los Angeles, T.
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Chapin, Henry A., Ayers Bk. Bldg., Jacksonville, Ill., 2.
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Cheever, Austin Walter, 510 Commonwealth Ave., Boston, 1.
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Clark, G. C., 1339 E. Capitol St., Washington, D. C., 9.
Clark, Wm. L., Medical Arts Bldg., 16th and Walnut, Philadelphia, 4, 7, 9.
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Collings, Howard P., Dugan-Stewart Bldg., Hot Springs, Ark., 2.
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Faulk, Robert W., Monroe, La.. 0.
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Field, G. J., Judge Bldg., Salt Lake City, 8.
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Foster, Howard M., 3969 Kennerly Ave., St. Louis, 2.
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Fox, Howard, 114 E. 54th St., New York City, 4, 5, 6, 7, 0, 1, 2.
Fraser, J. Frank, 338 E. 26th St., New York, 7, 1.
Frear, Edwin D., Farmers Trust Bldg., Sioux City, Ia., 1.
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Hissem, R. W., Bitting Bldg., Wichita, Kan., T.
Hix, J. B., Altus, Okla., T.
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Holley, A. S., Goggan Bldg., Houston, Tex., 0.

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